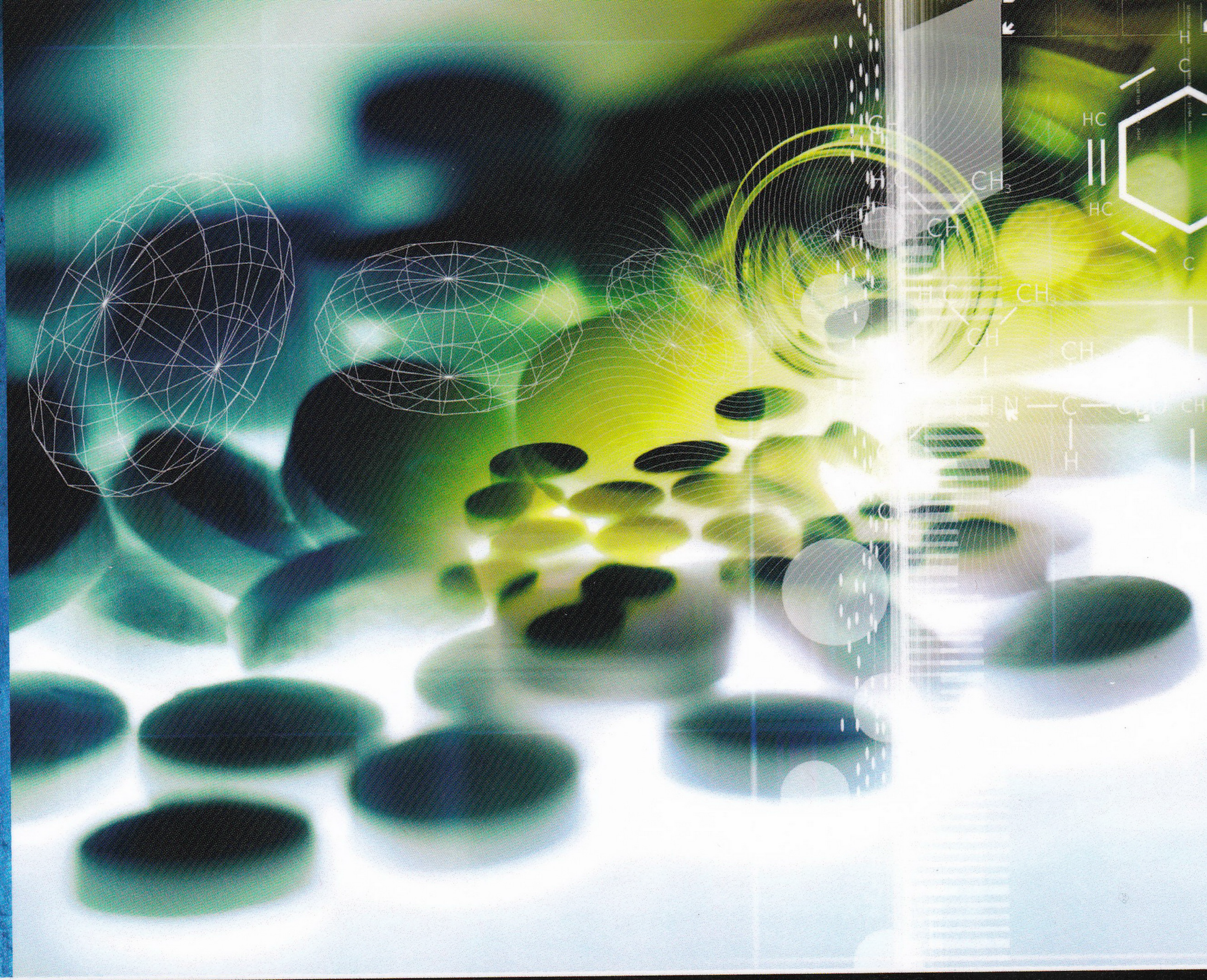

Pharmacology

USMLE STEP 1

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USMLE Step 1

Pharmacology

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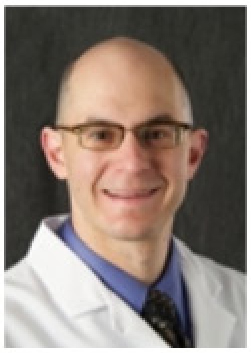

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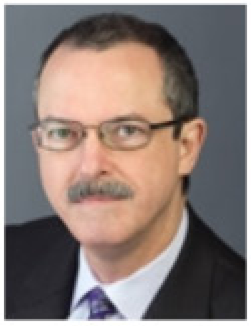

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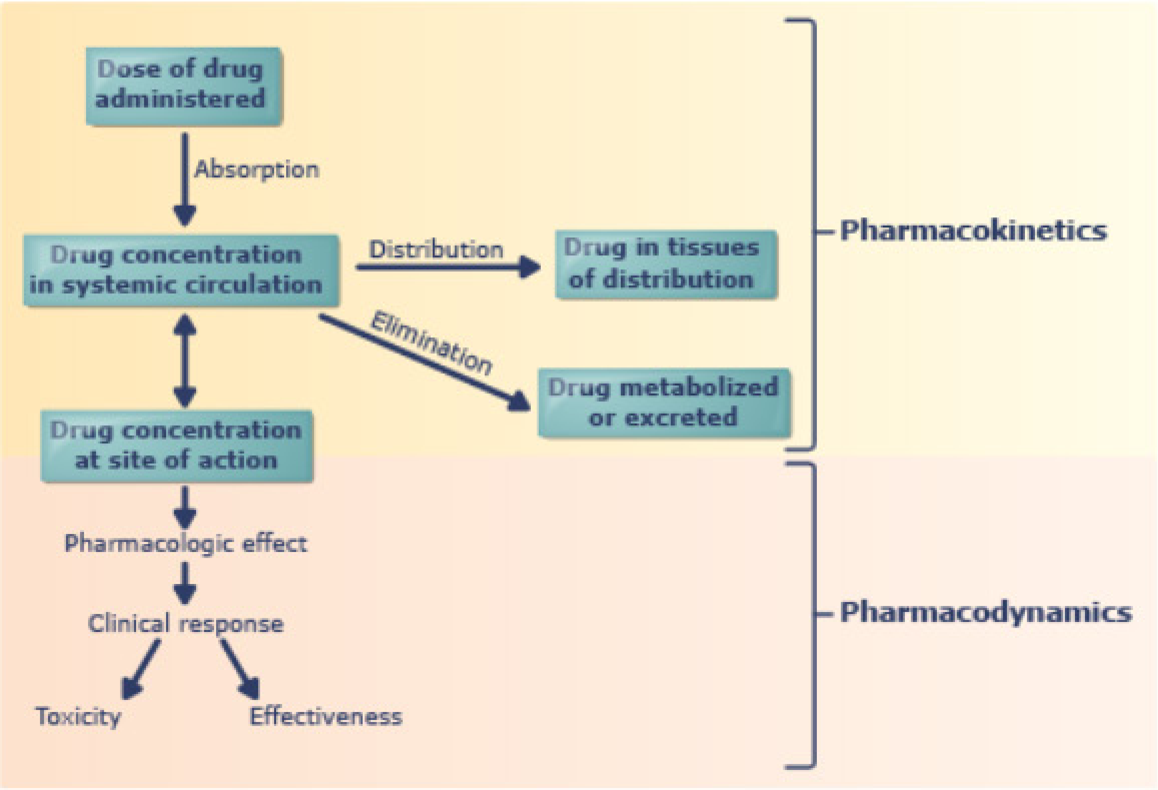
CHAPTER 1 Principles of Pharmacology

1 Overview of Pharmacology

Pharmacology, the scientific study of drugs, is often broadly divided into pharmacokinetics and pharmacodynamics. As Figure 1-1.0 shows, pharmacokinetics concerns the movement of drugs through the human body to their intended target. Pharmacodynamics addresses the mechanism of action and effect of drugs after the drugs reach their intended target.


Dose of drug administered
Absorption
Drug concentration in systemic circulation
Distribution
Drug in tissues of distribution
Elimination
Drug metabolized or excreted
Drug concentration at site of action
Pharmacokinetics
Pharmacologic effect
Clinical response
Toxicity
Effectiveness
Pharmacodynamics

▲**Figure 1-1.0** Pharmacokinetics and Pharmacodynamics

2 USMLE Step 1

Pharmacology is an important subject for USMLE Step 1.® High-yield areas include:

- **Generic Drug Names:** Step 1 mainly uses generic drug names (e.g., phenytoin) instead of trade names (Dilantin). Occasionally, both generic and trade names are used in the stem of questions, but the options will be generic drug names.
- **Pharmacodynamics:** Mechanism of action is often tested in Step 1, less commonly in Steps 2 or 3.
- **Adverse Effects:** Emphasis is on unique adverse effects. Classic examples include pulmonary fibrosis (bleomycin, amiodarone), Coombs positive hemolytic anemia (α-methyldopa), aplastic anemia (chloramphenicol), and red-colored urine (rifampicin, doxorubicin).

USMLE® Key Concepts

For Step 1, you must be able to:

- Explain the differences between pharmacokinetics and pharmacodynamics.
- Describe the roles distribution, absorption, metabolism, and elimination play in pharmacokinetics.
- Describe the roles affinity, potency, and efficacy play in pharmacokinetics.
- Define different types of antagonists, including competitive, non-competitive, irreversible, chemical, and physiologic.

- **Autonomic Drugs:** Emphasis in Step 1 is focused on problems that require interpretation of physiologic data. Pay particular attention to drugs acting on the adrenergic system.
- **Antibiotics:** Step 1 questions increasingly require interpretation of data (e.g., Gram stain) as opposed to straight memory recall. A common pitfall to avoid is to pick an antibiotic that covers the organism but is not appropriate to the clinical situation. An example would be using gentamicin (IV antibiotic with potential toxicity) for treatment of a routine urinary tract infection. Even though gentamicin would cover a gram-negative (e.g., *E. coli*) urinary tract infection, a better choice would be an oral drug like trimethoprim-sulfamethoxazole or ciprofloxacin. Also pay attention to antibiotic resistance mechanisms.
- **Central Nervous System (CNS) and Cardiovascular Drugs:** High-yield areas for Step 1 include CNS drugs ranging from antidepressants to general anesthetics, and cardiovascular drugs like antihypertensives and drugs for heart failure.
- **Drug-Drug Interactions:** Drugs that commonly cause adverse interactions are inducers (rifampin, phenobarbital, phenytoin) and inhibitors (cimetidine, erythromycin) of P450 enzymes.
- **Pharmacogenetics:** Genetic variation in drug response is an emerging field that has been increasingly tested on Step 1. High-yield examples include genetic variation in cytochrome P450 2C9 (affecting warfarin) and UGT1A1 (affecting the chemotherapy drug irinotecan). Note that both pharmacokinetics and pharmacodynamics can be influenced by genetic variation in drug response.
- **Focus on Established Drugs:** Step 1 questions are by nature a few years behind clinical practice, making it low yield to study drugs introduced within the last year. Focus on established drugs and newer drugs only if they have significant clinical impact. A recent example of the latter is imatinib (Gleevec), which allows for better treatment of chronic myelogenous leukemia (CML), a disease that previously had been difficult to manage. Step 1 questions on imatinib appeared fairly soon after the drug was introduced to clinical practice.

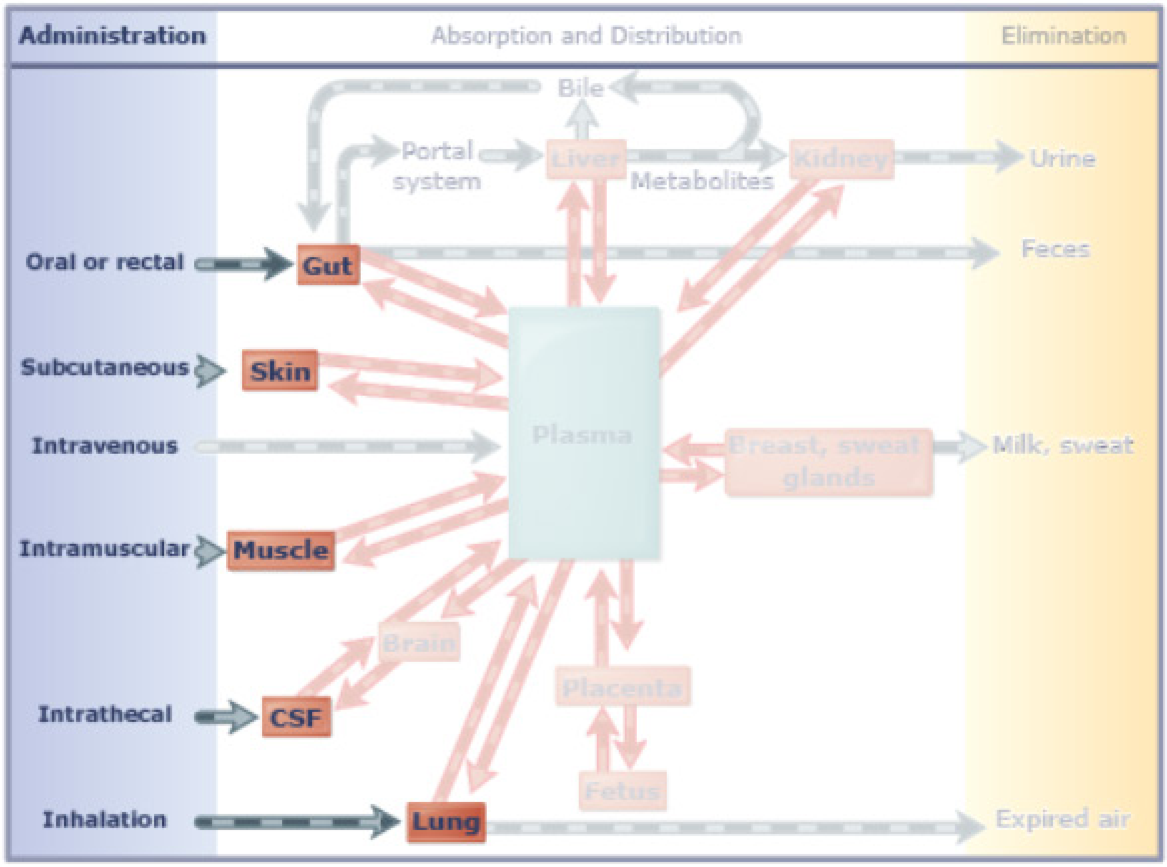
3 Pharmacokinetics

3.1 Overview of Pharmacokinetics

Pharmacokinetics, the movement of pharmaceuticals through the human body, includes the processes of absorption, distribution, metabolism, and excretion ("ADME"). One way to think about pharmacokinetics is "What happens to the drug after it is administered?" For Step 1, the highest-yield aspect of pharmacokinetics is metabolism, which also involves many clinically relevant cases of drug-drug interactions and pharmacogenetics.

3.2 Routes of Drug Administration

The way a drug is administered (enters the body) influences its pharmacokinetics. There are multiple means by which drugs can be administered.


Administration
Absorption and Distribution
Elimination
Bile
Portal system
Liver
Metabolites
Kidney
Urine
Oral or rectal
Gut
Feces
Subcutaneous
Skin
Intravenous
Plasma
Breast, sweat glands
Milk, sweat
Intramuscular
Muscle
Brain
Placenta
Intrathecal
CSF
Fetus
Inhalation
Lung
Expired air

▲**Figure 1-3.2** Routes of Administration

3.2.1 Oral

This is the most common route of administration. Drug absorption depends on uptake from the gastrointestinal tract. Oral administration is also affected by first-pass metabolism in the liver.

3.2.2 Intravenous

This is a form of parenteral administration that involves piercing the skin or mucous membranes. The intravenous route introduces the drug directly into the venous circulation, but is more invasive than other forms of administration.

▼Table 1-3.2 Routes of Administration

Route	Characteristics
Oral	Easiest for patients; bioavailability limited by first-pass effect
Intravenous	Rapid absorption; invasive
Intramuscular	Slow absorption; potentially painful
Subcutaneous	Only small volumes feasible; potentially painful
Sublingual	Easy; avoids first-pass effect; limited range of agents available for this route
Transdermal	Slow, steady absorption; no first-pass effect; prolonged delivery
Intrathecal	Highly specialized; direct delivery to CNS; invasive
Rectal	Bioavailability limited by first-pass effect
Inhalation	Rapid absorption; no first-pass effect

Katsung, Bertram et al, *Basic and Clinical Pharmacology*, 12th ed. © 2012 The McGraw-Hill Companies, Inc.

3.2.3 Intramuscular

Intramuscular injection, another form of parenteral administration, can be clinically helpful in two main situations. Some drugs can be rapidly injected intramuscularly when intravenous access may be difficult. Examples include treatment of epileptic crisis with fosphenytoin or hypoglycemia with glucagon. Intramuscular injection can also be used for depot injections of drugs that get slowly absorbed over days to weeks such as testosterone esters and some antipsychotics.

3.2.4 Subcutaneous (Under the Skin)

Subcutaneous injection is commonly used for injection of heparin and insulin.

3.2.5 Sublingual (Under the Tongue)

Sublingual administration avoids first-pass metabolism. This is used for nitroglycerin and some migraine medications.

3.2.6 Transdermal (Skin Patch)

Transdermal administration can be used for steady absorption of a drug over 1–2 days. Examples include nitroglycerin, testosterone, and fentanyl.

3.2.7 Intrathecal

Intrathecal is a specialized route of administration that directly delivers the drug to the subarachoid space of the central nervous system. This can be used for chemotherapy and some pain medications.

3.2.8 Rectal

Rectal administration is relatively uncommon and is used either to treat colorectal disorders (e.g., ulcerative colitis) or to avoid oral or intravenous administration. For example, diazepam can be administered rectally in cases of status epilepticus (epilepsy crisis). Like oral administration, rectal administration is affected by first-pass metabolism due to venous drainage of the distal GI tract into the portal circulation.

3.2.9 Inhalation

This form of administration is used to deliver some medications for pulmonary conditions. Inhaled corticosteroids are widely used for asthma treatment and have the advantage of limiting systemic drug exposure compared to oral or intravenous administration. Inhalation is also used for the volatile general anesthetics. Due to the high blood flow reaching the lungs, inhaled general anesthetics can rapidly induce general anesthesia.

3.3 Absorption

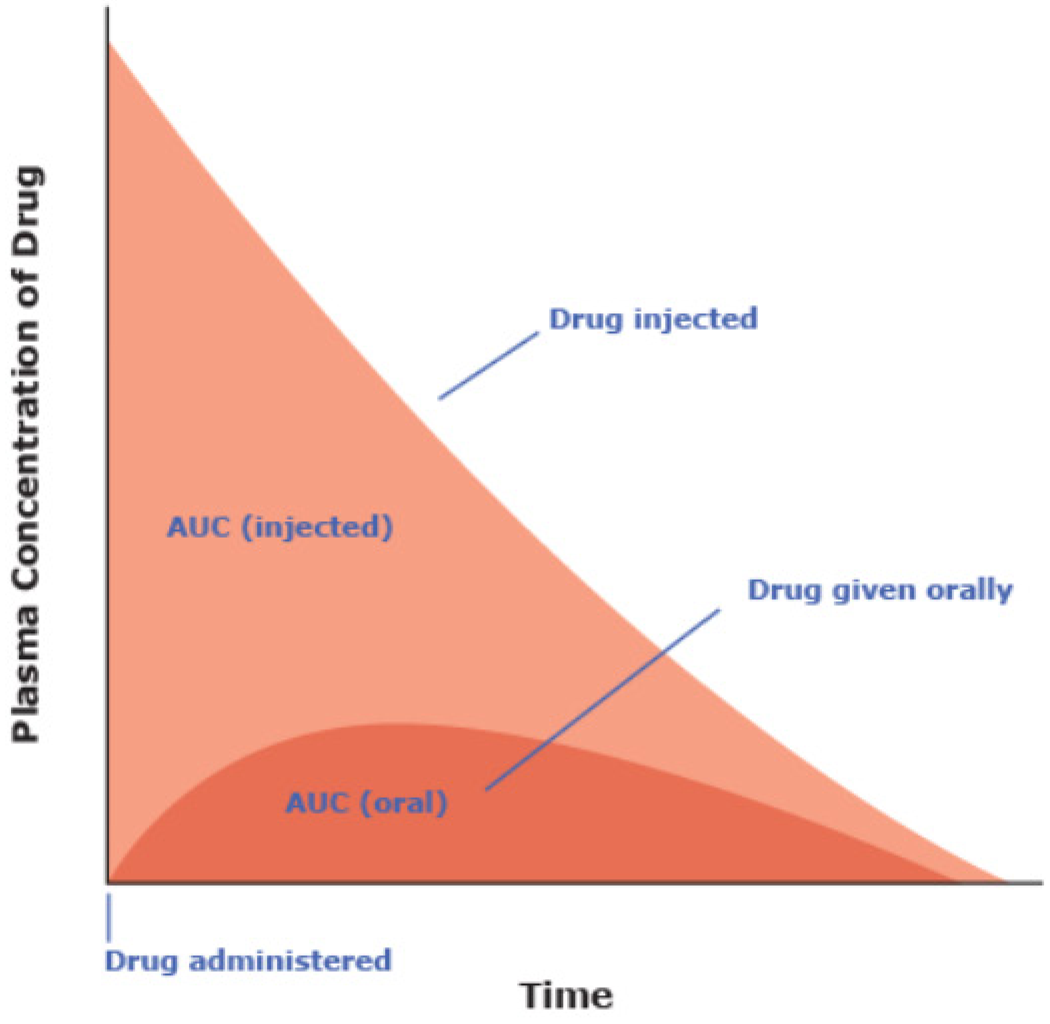
Absorption is the process by which drugs reach the venous (systemic) circulation. This may occur via the GI tract for orally administered drugs or other routes such as through the skin in transdermally applied drugs.

3.3.1 First-Pass Effect

The first-pass effect occurs with drugs administered by the oral and rectal routes. When drugs are given orally and rectally, they are absorbed into the portal circulation, which passes through the liver. If the drug is metabolized by the liver in this "first pass," the amount of parent drug reaching the venous circulation is reduced.

3.3.2 Bioavailability

Bioavailability is a measure of how much drug reaches the systemic circulation following administration. It is expressed either as percent or as a fraction (F) between 0 and 1. *Poor absorption or a strong first-pass effect or both will reduce bioavailability.* Intravenous administration by definition results in a bioavailability of 100% (F=1). Bioavailability is sometimes also measured as the "area under the curve" (AUC) in a graph of plasma concentration (y-axis) vs. time. A larger AUC indicates more total drug entering the venous circulation.



$$\text{Bioavailability} = \frac{\text{AUC oral}}{\text{AUC injected}} \times 100$$

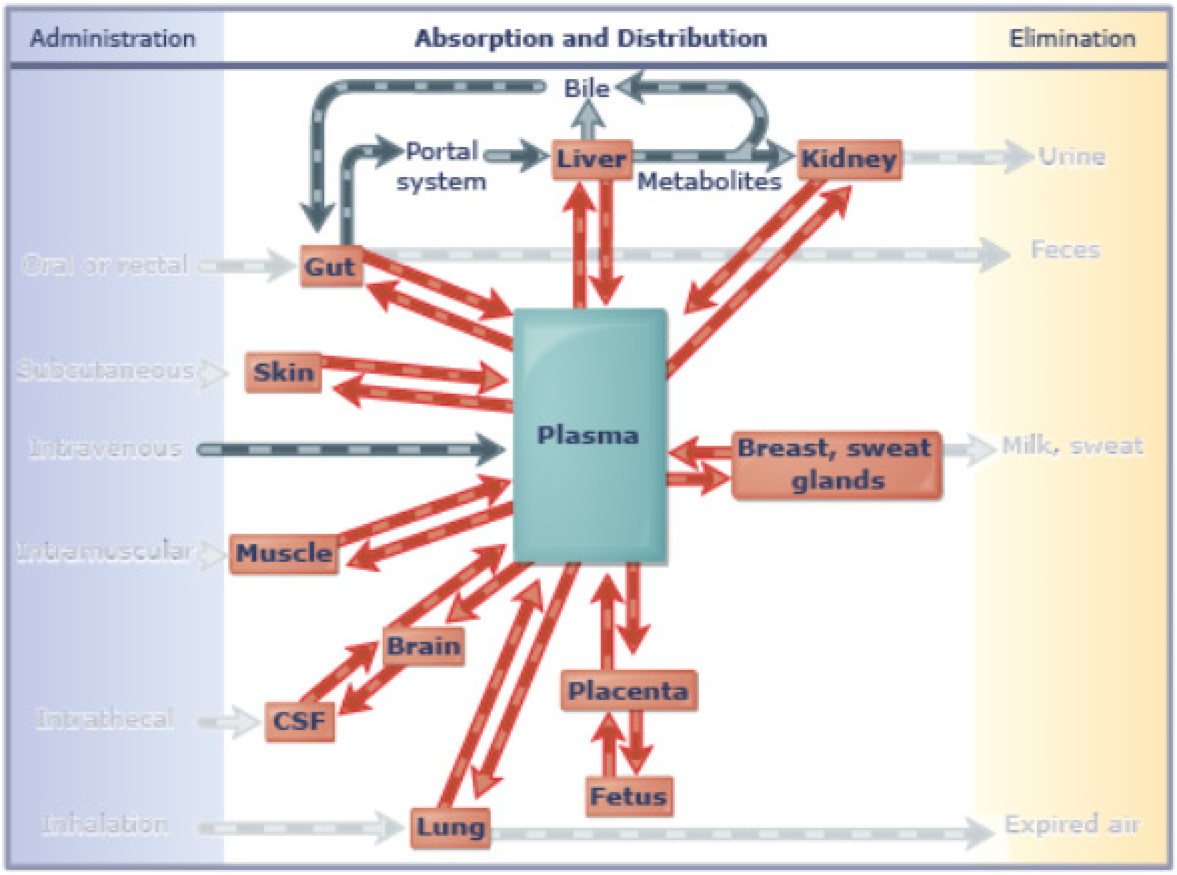
▶ **Figure 1-3.3A** Bioavailability

3.3.3 Bioequivalence

Bioequivalence is a measure of the bioavailability and rate of absorption of different formulations of the same drug. Two drugs are said to be bioequivalent if they have essentially the same bioavailability and absorption rate. However, for drugs with a low therapeutic index and high risk of toxicity (e.g., digoxin, lithium, warfarin), it is advisable to stay with the same formulation because even though two different formulations may be bioequivalent within a certain margin of variation, they are likely not absolutely identical in bioavailability and absorption. As a result, switching patients from one formulation to another can lead to problems.

3.3.4 Absorption and Drug-Drug or Drug-Food Interactions

Some drugs or food interfere with drug absorption. A classic example is the reduced absorption of the antibiotic tetracycline through the GI tract in the presence of milk or antacids. The cations in the milk or antacids such as Ca^{2+}, Mg^{2+}, and Al^{3+} chelate (bind) the tetracycline, forming an insoluble complex that cannot be absorbed by the GI tract.


Administration
Absorption and Distribution
Elimination
Bile
Portal system
Liver
Metabolites
Kidney
Urine
Oral or rectal
Gut
Feces
Subcutaneous
Skin
Intravenous
Plasma
Breast, sweat glands
Milk, sweat
Intramuscular
Muscle
Brain
Intrathecal
CSF
Placenta
Fetus
Inhalation
Lung
Expired air

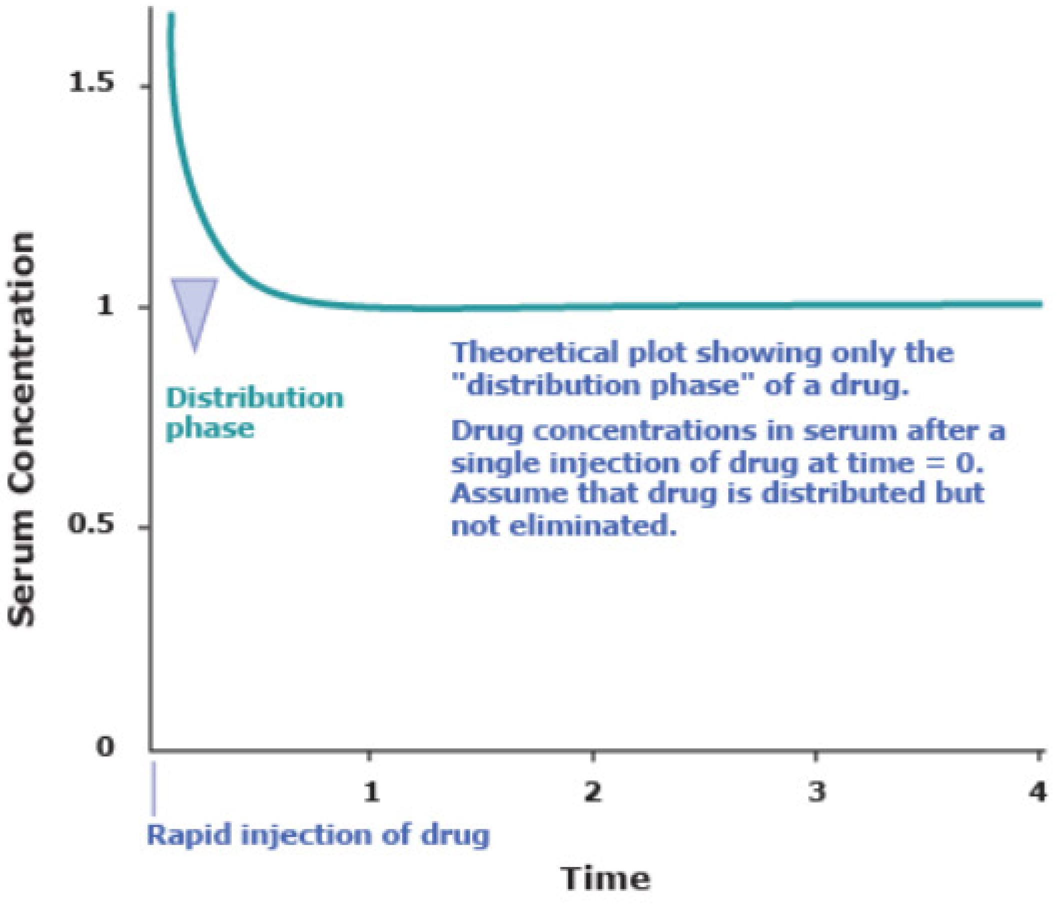
▲**Figure 1-3.3B** Absorption and Distribution

3.4 Distribution

Distribution is the process by which drugs move from the systemic circulation into organs and tissues. Drugs may distribute widely into many organs and tissues or more narrowly. Distribution is influenced by a number of factors, including lipid solubility, rate of blood flow to the target tissues, and binding of the drug to plasma proteins.

3.4.1 Distribution Phase of a Drug

When a drug is administered intravenously and plasma concentrations are measured over time, there is usually an initial fall in plasma concentration. This fall is mostly due to distribution of the drug to tissues/organs (and thus not in the plasma anymore), not due to the elimination of drug from the body.



▲**Figure 1-3.4A** Distribution Phase

3.4.2 Placental Barrier

In pregnancy, drugs administered to the mother can cross the placenta and affect the fetus. Small (molecular weight 250–500 Daltons) and lipophilic drugs usually cross the placenta easily. Charged molecules do not cross. A classic contrast between two pharmacologically similar drugs is heparin and warfarin. Heparin is a charged, large-molecular-weight drug that does not cross the placenta. Warfarin is a small, lipophilic drug that crosses the placenta and causes birth defects. Heparin is therefore the anticoagulant of choice in pregnancy.

3.4.3 Blood-Brain Barrier

As with the placental barrier, small and lipophilic drugs cross into the central nervous system (CNS). The blood-brain barrier is disrupted in acute meningitis and some inflammatory processes of the CNS. This can lead to higher level of transport of certain medications into the CNS.

3.4.4 Plasma Protein Binding

Many drugs bind to plasma protein such as *albumin* in the circulation. Only unbound drugs are able to cross plasma membranes and be biologically "active" and activate their targeted receptors. Binding of drugs to plasma proteins is usually of little clinical significance unless greater than 60%. For such drugs, hypoalbuminemia can cause significant changes in free drug concentrations. An example of a drug with high plasma protein binding is phenytoin. For phenytoin and other drugs with high degrees of plasma protein binding, it can be useful to measure "free" (unbound) drug concentrations to determine how much biologically active drug is present in the plasma.

3.4.5 Volume of Distribution

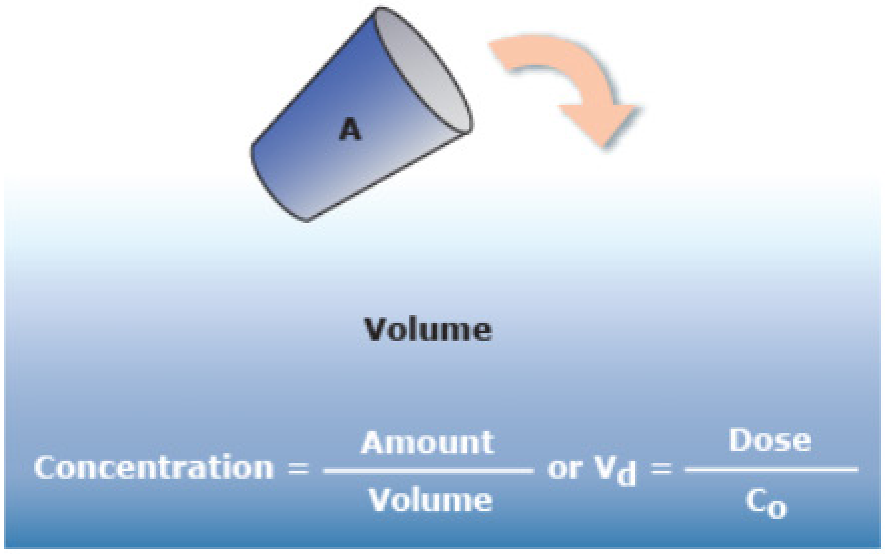
The volume of distribution (V_d) is a measure of how widely a drug distributes in the body. A theoretic volume, V_d, is often referred to as "apparent" volume of distribution. The equation for volume of distribution is worth knowing and is:

V_d = dose/C_0 [where C_0 is plasma concentration of drug at time zero]

Consider the following example. A patient is admitted to the hospital for pneumonia due to *Pseudomonas aeruginosa*. The antibiotic ciprofloxacin is ordered. The V_d of ciprofloxacin is 40 L. If you wish to give an IV loading dose to achieve the therapeutic plasma concentration of 4 mg/L rapidly, how much should be given?

$$\text{Loading dose} = V_d \times C_0 = 40\ \text{L} \times 4\ \text{mg/L} = 160\ \text{mg}$$

For some drugs, V_d corresponds to water "compartments" in the body. For example, a drug like heparin that stays in the plasma and does not distribute to any organs/tissues has a V_d of ~3 L in a typical adult, which approximates the water in the plasma compartment. Drugs with very high apparent V_d bind extensively to tissues. The small amount of drug left in the plasma makes it appear as if the drug has distributed into a large volume of water. Lipid soluble drugs like ETOH (with a large V_d) do not generally stay in the plasma. Further, performing hemodialysis would not be an effective way to clear drugs with a large V_d because those drugs are not generally found in the plasma.



▲**Figure 1-3.4B** Volume of Distribution

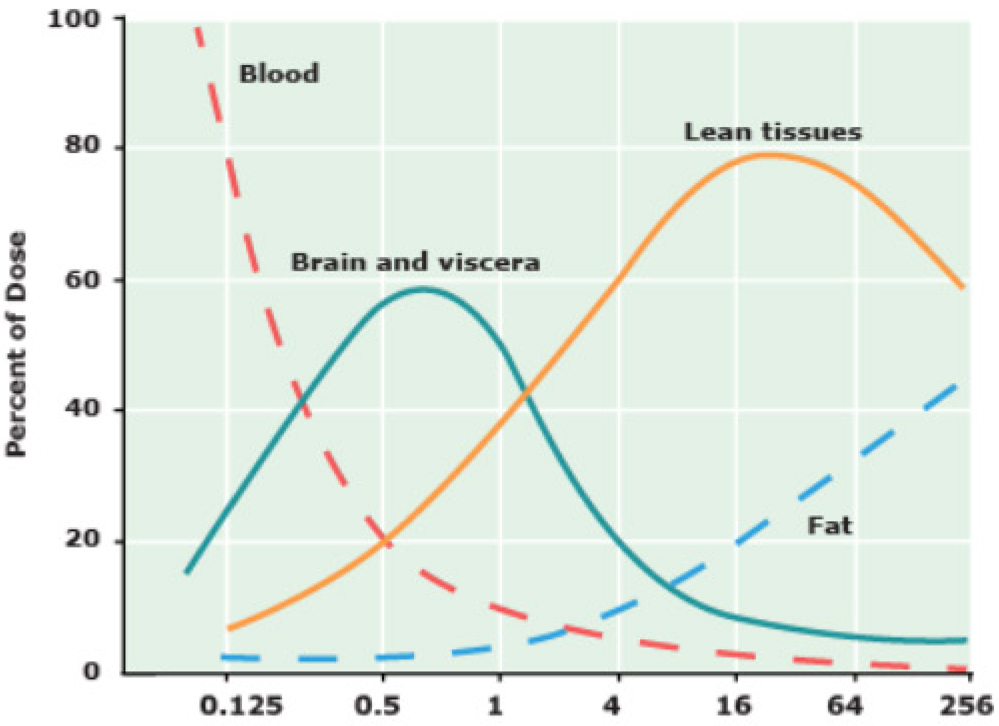
▼**Table 1-3.4** Volume of Distribution: A Comparison

Drug	Volume of Distribution (l/kg)*
Chloroquine	200
Nortriptypline	20
Digoxin	7
Propranolol	4
Phenytoin	0.65
Theophylline	0.50
Gentamicin	0.25
Aspirin	0.14
Warfarin	0.10

*Drugs with very high V_d distribute out of plasma to tissues

3.4.6 Redistribution of Lipid-Soluble Drugs

Redistribution is a phenomenon that is clinically important with the lipid-soluble general anesthetics thiopental and propofol. These two drugs distribute first from the systemic circulation into the brain (target organ), which has high blood flow. Once in the brain, they "redistribute" to other tissues with slower blood flow such as muscle and fat. When thiopental and propofol are used for anesthesia and the drug delivery is stopped, the patient comes out of anesthesia relatively quickly not because the drug is eliminated from the body, but mainly because the drug redistributes from brain to other tissues. However, redistribution can cause a *"hangover"* effect in that repeated doses of drugs lead to accumulation of drugs in muscle and fat, which can then go back into the brain. Obese patients receiving extended doses of propofol (as is used for sedation while intubated) are especially prone to this and may take hours to days to fully remove the drug from the body.



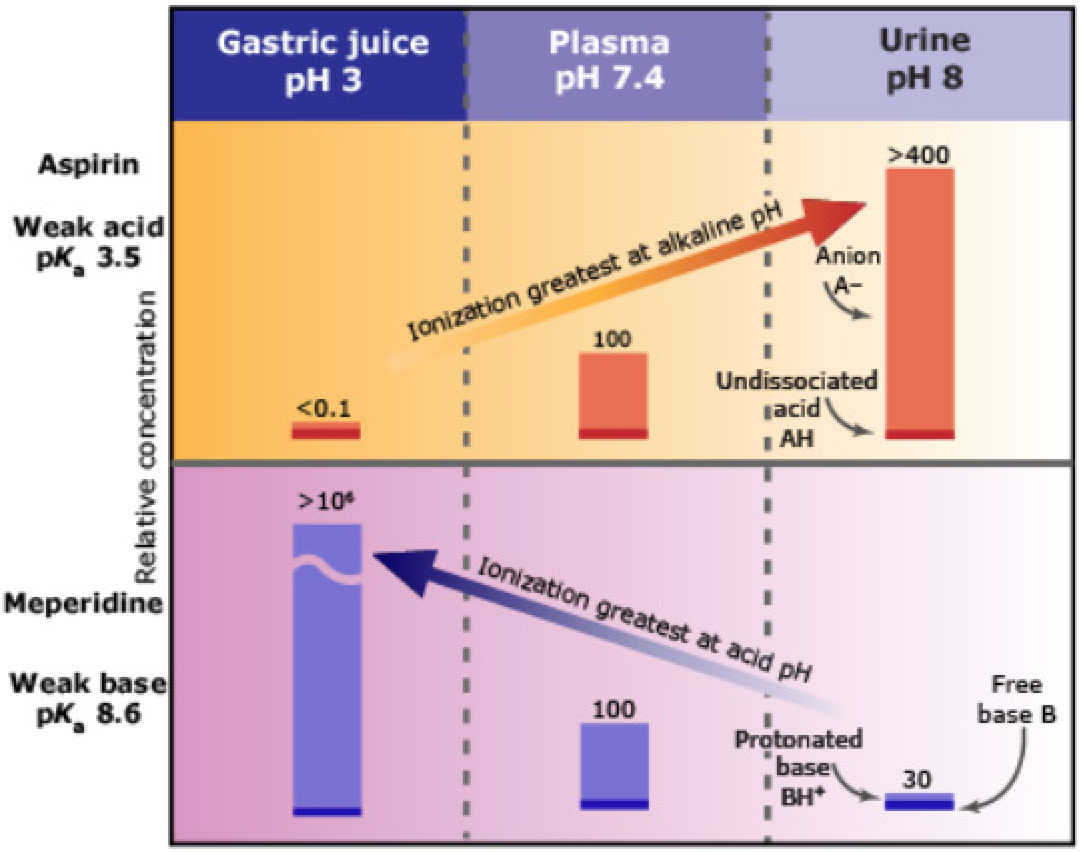
▲**Figure 1-3.4C** Redistribution of Thiopental

3.5 Ionization of Drugs

Many drugs are weak acids or weak bases. These drugs are subject to ionization, which can affect their absorption and elimination. A key point to remember is that *ionized (charged) drugs are not absorbed efficiently through the GI tract* or other bio-membranes, including the plasma membranes of cells. In contrast, non-ionized drugs are absorbed well passively. Drugs are ionized or non-ionized based on the pH of the local environment (for example, low pH in lumen of stomach, pH of ~7 in the ileum) and the pK_a of the drug (the pH at which the molecule is 50% ionized and 50% non-ionized). Ionization is not an issue for drugs that are neither acids nor bases.

▼**Table 1-3.5** Henderson-Hasselbalch Table

$pH - pK_a$	−3	−2	−1	0	+1	+2	+3
Weak acid: % non-ionized	99.9	99	90	50	10	1	0.1
	More drug crosses the plasma membrane			←		Less drug crosses the plasma membrane	
Weak base: % non-ionized	0.1	1	10	50	90	99	99.9
	More drug crosses the plasma membrane			→		Less drug crosses the plasma membrane	



▲**Figure 1-3.5** Theoretical Partition of Weak Acid (Aspirin) and Weak Base (Meperidine)

3.5.1 How Drug Ionization Affects Renal Clearance

Both ionized and non-ionized forms of drugs generally pass through the glomerulus. But only non-ionized forms can be reabsorbed back into venous circulation from the renal tubules. This can be a problem for drug overdoses such as aspirin (salicylates) in that the drug is not cleared in the urine, but instead gets back into the bloodstream.

3.5.2 Drug Trapping in the Urine

For some drug overdoses, increasing ionization of the drug can be clinically useful in "ion trapping" the drug in the urine by making it ionized and avoiding diffusion back into the venous circulation. *Alkalinizing urine by intravenous sodium bicarbonate ($NaHCO_3$) increases ionization of weak acids.* This is used to treat salicylate overdose as well as the high uric acid seen in the tumor lysis syndrome. Acidification of urine can theoretically be used to treat overdoses of weak bases, but this is essentially never done clinically.

3.6 Drug Metabolism

Drug metabolism, also known as biotransformation, is the process by which drug molecules are converted by enzymes into metabolites. Generally, drug metabolites are more water soluble and more easily excreted than the parent drug. Compared to the parent drug, metabolites may have similar activity ("active" metabolites) or little or no activity ("inactive" metabolites). Metabolites may also be more toxic than the parent drug, of which there are many examples, such as meperidine (Demerol), whose metabolite *normeperidine can cause neurotoxicity and seizures.*

Clinical Application

Local anesthetics, including lidocaine, are weak bases, with pK_a values of approximately 8–9. This means that 50% of lidocaine will be ionized and 50% non-ionized at a pH between 8 and 9. At a physiologic pH of approximately 7, roughly 1–10% of the lidocaine molecules will be non-ionized and able to cross the plasma membrane of nerve cells and block sodium channels. However, if lidocaine is injected into an infected tissue, such as an abscess, with a lower pH of approximately 5, less than 0.1% of the lidocaine molecules will be non-ionized, making it difficult to achieve local anesthesia.

$$\begin{aligned}\log\left(\frac{HB^+}{B}\right) &= pK_a - pH\\ &= 8 - 7\\ \frac{HB^+}{B} = \frac{10}{1} &= \frac{90\%\text{ ionized}}{10\%\text{ unionized}}\end{aligned}$$

versus

$$\begin{aligned}\log\left(\frac{HB^+}{B}\right) &= pK_a - pH\\ &= 8 - 5\\ \frac{HB^+}{B} = \frac{1{,}000}{1} &= \frac{99.9\%\text{ ionized}}{0.001\%\text{ unionized}}\end{aligned}$$

3.6.1 Prodrugs

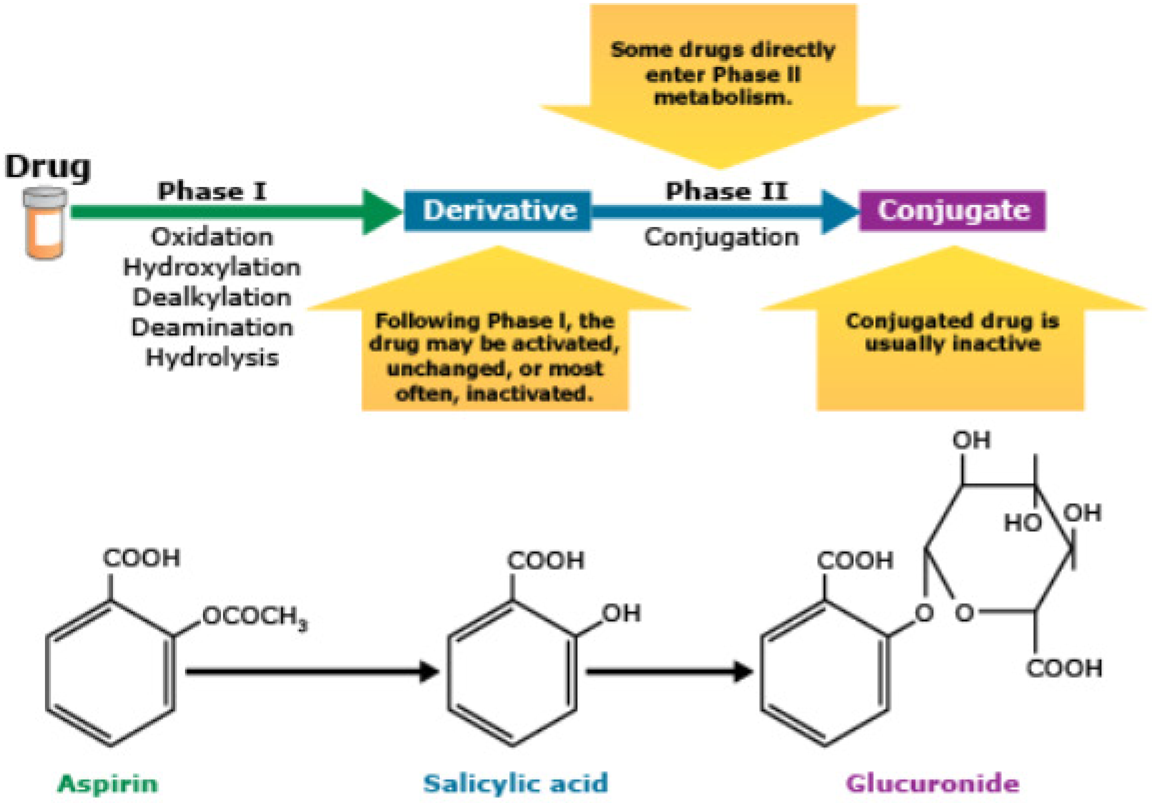
Prodrugs are a special case in which the parent drug *must* be converted to its active form to have its therapeutic effect on the body. Examples include azathioprine (prodrug of 6-mercaptopurine), codeine (prodrug of morphine), and valacyclovir (prodrug of acyclovir).

3.6.2 Phases of Drug Metabolism

Drug metabolism is often divided into phase I and II.

Phase I Drug Metabolism This phase involves modification of the drug molecule by oxidation, reduction, and hydrolytic reactions. The most common enzymes involved in phase I are the *cytochrome P450 (CYP) enzymes.*

Phase II Drug Metabolism This phase involves conjugation of the drug molecule with enzymes known as transferases. Examples of conjugation reactions are acetylation, glucuronidation, glutathionylation, and sulfation. Phase II reactions usually result in inactive, more water-soluble metabolites. There are few cases of drugs with active phase II metabolites (e.g., morphine-6-glucuronide).


Some drugs directly enter Phase II metabolism.
Drug
Phase I
Derivative
Phase II
Conjugate
Oxidation
Hydroxylation
Dealkylation
Deamination
Hydrolysis
Conjugation
Following Phase I, the drug may be activated, unchanged, or most often, inactivated.
Conjugated drug is usually inactive
COOH
OCOCH3
OH
O
HO
Aspirin
Salicylic acid
Glucuronide

▲**Figure 1-3.6A** Two Phases of Metabolism

3.6.3 Pharmacogenetics Involving Drug Metabolism

Many of the clinically important examples of pharmacogenetics involve enzymes involved in drug metabolism, especially the cytochrome P450 enzymes discussed below. *Slow metabolizers* have a genetic difference that results in slower-than-normal drug metabolism, often due to two copies (alleles) of the gene that have little or no enzymatic activity. *Ultra-rapid metabolizers* have much faster-than-average drug metabolism, often due to multiple copies of the gene (i.e., more than the two alleles).

3.6.4 Cytochrome P450 (CYP) Enzymes

CYP enzymes are a major system of enzymes involved in phase I metabolic reactions. CYP enzymes are found in the liver, GI tract, lungs, and kidney, in all animals, and even in other organisms such as fungi.

The major clinically important drug-metabolizing human CYPs are:

- CYP3A4
- CYP2D6
- CYP2C9
- CYP2C19

CYP3A4 The "workhorse" is the most highly expressed CYP in human liver and is estimated to metabolize over 50% of prescribed drugs. Compounds metabolized by CYP3A4 include:

- Steroids (estradiol, testosterone)
- Vitamin D
- Immunosuppressants (cyclosporine, tacrolimus)
- HIV protease inhibitors
- Calcium channel blockers
- Statins

CYP3A4 is often involved in drug-drug interactions. As described below, there are drugs that induce (increase) or inhibit (decrease) CYP3A4 activity.

CYP2D6 This enzyme metabolizes a number of clinically important drugs, including:

- Antidepressants (fluoxetine, paroxetine, amitriptyline, imipramine)
- Antipsychotics (chlorpromazine, haloperidol, risperidone)
- Beta-blockers (metoprolol, propranolol)
- Codeine (converted to morphine)
- Tamoxifen (converted to active metabolites)

CYP2D6 shows genetic variation among individuals. "Slow metabolizers" are roughly 5% of the population and have little or no CYP2D6 activity. This can lead to:

- Toxicity for some drugs (such as amitriptyline) due to inability to metabolize.
- Lack of benefit from prodrugs like codeine that depend on conversion.

"Ultra-rapid metabolizers" are roughly 5% of the population and have greater-than-normal CYP2D6 activity, leading to:

- Rapid inactivation of drugs (such as fluoxetine) that are primarily metabolized by CYP2D6.
- Potential toxicity from codeine due to rapid conversion to morphine.

CYP2C9 This enzyme is important mainly as the metabolizer of warfarin. CYP2C9 slow metabolizers are at risk of bleeding if given standard warfarin doses. This could be seen as an excessively high prothrombin time (or INR, international normalized ratio) after starting warfarin therapy.

CYP2C19 This enzyme metabolizes citalopram, diazepam, and phenytoin. CYP2C19 also converts clopidogrel (Plavix) to an active metabolite. CYP2C19 poor metabolizers can have "clopidogrel resistance."

3.6.5 Inducers of CYP Enzymes

Certain drugs cause the liver to increase expression of CYP enzymes. This leads to increased metabolism of drugs and endogenous compounds (such as vitamin D and estrogens) metabolized by CYP enzymes. The most common inducers of CYP enzymes are the following drugs:

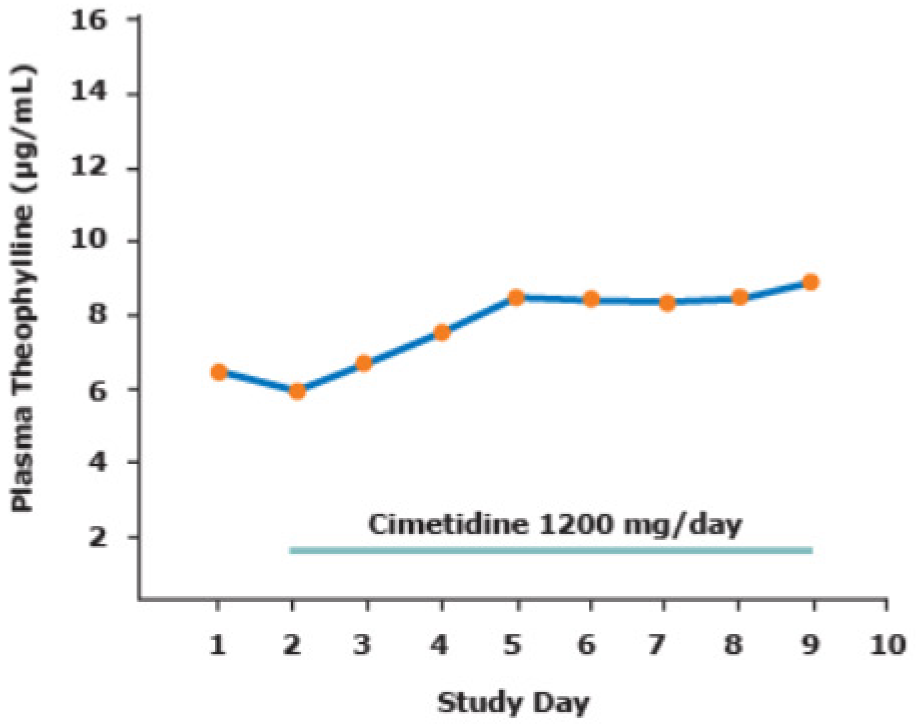
- Rifampin
- Phenytoin
- Carbamazepine (also able to induce its own metabolism—"auto-induction")
- St. John's wort (herbal antidepressant)
- Phenobarbital
- Barbiturates
- Glucocorticoids

3.6.6 Inhibitors of CYP Enzymes

Some drugs inhibit (block) the ability of CYP enzymes to metabolize other drugs. Common CYP inhibitors include the following:

- Ketoconazole (and to a lesser degree other azoles)
- Cimetidine (Tagamet)
- Erythromycin
- Omeprazole and other proton pump inhibitors (inhibits CYP2C19)
- Trimethoprim-sulfamethoxazole (inhibits CYP2C9)
- Grapefruit juice (inhibits CYP3A4)—avoid in transplant patients due to interactions with cyclosporine and tacrolimus

Ketoconazole, cimetidine, and erythromycin are most prone to causing drug-drug interactions since they inhibit multiple CYPs. Ranitidine (Zantac) does not inhibit CYPs and is thus generally a better alternative to cimetidine for acid blocking therapy.



▲ **Figure 1-3.6B** CYP Inhibition by Cimetidine Causing Increase in Plasma Theophyline Concentration

Clinical Application

Classic inducer case #1: Woman becomes pregnant despite taking oral contraception because she is also taking the CYP inducer carbamazepine (Tegretol), which increased metabolism of the estrogen in the birth control pill.

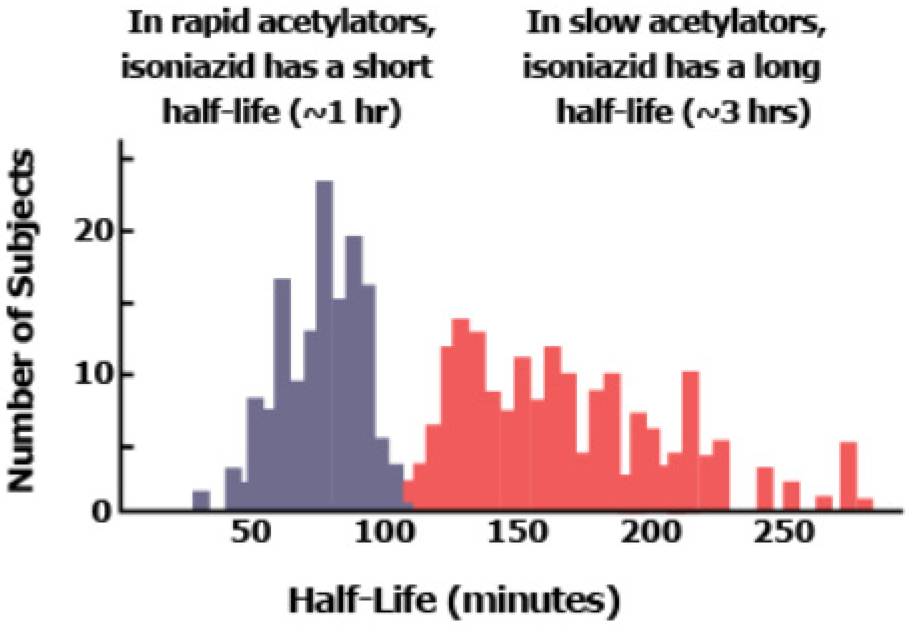
Classic inducer case #2: Patient taking tacrolimus following organ transplant to prevent rejection but starts taking St. John's wort, which leads to more rapid metabolism of the tacrolimus and rejection of the organ.

3.6.7 Glucuronidation

Glucuronidation is a common form of phase II metabolism catalyzed by UGT (UDP-glucuronosyltransferase) enzymes. Drugs that are glucuronidated include chloramphenicol and morphine. *Infants have limited ability to glucuronidate* and can experience toxicity from drugs that are mainly cleared by glucuronidation. This underlies the adverse *gray-baby syndrome* seen when infants are given the antibiotic chloramphenicol.

3.6.8 Acetylation

Hydralazine, procainamide, and isoniazid are metabolized by acetylation. Genetic variation can result in fast acetylators (rapid metabolism) and slow acetylators (slow metabolism). Slow acetylators are more prone to a lupus-like syndrome when prescribed hydralazine, procainamide, and isoniazid.



▲**Figure 1-3.6C** Fast vs. Slow Acetylators

3.6.9 Sulfation

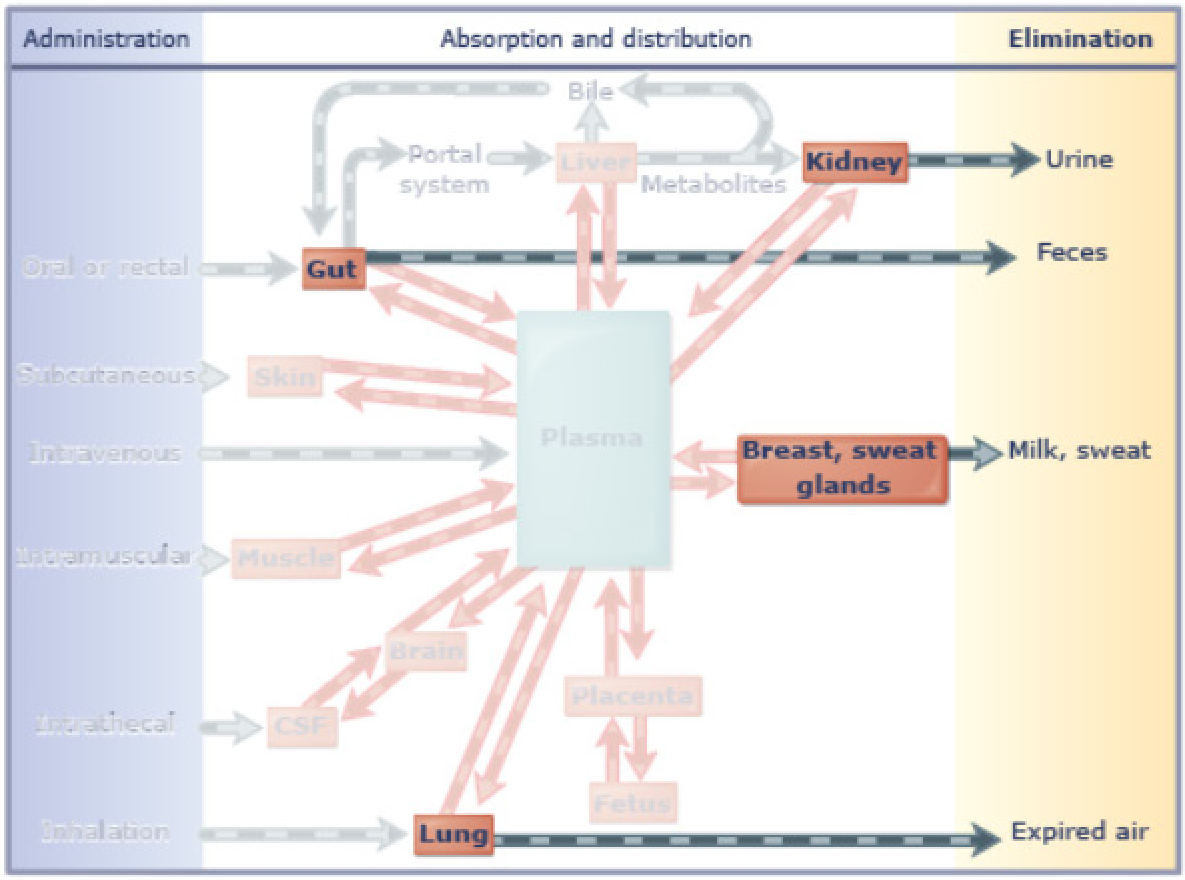
Sulfation is a relatively uncommon form of drug conjugation. An example of a drug that is sulfated is minoxidil. Steroids may also be sulfated, as in conjugated equine estrogens used as estrogen hormone replacements.

3.6.10 Glutathionylation

Glutathionylation is important in acetaminophen metabolism. Overdose of acetaminophen depletes glutathione, and acetaminophen may be converted to a toxic metabolite that can damage the liver. The antidote for acetaminophen overdose is N-acetylcysteine, which regenerates glutathione.

3.7 Elimination of Drugs

Elimination is the process of removal of drugs from the body. Major modes of drug elimination are via the kidney (renal), liver, lungs, and sweat glands.

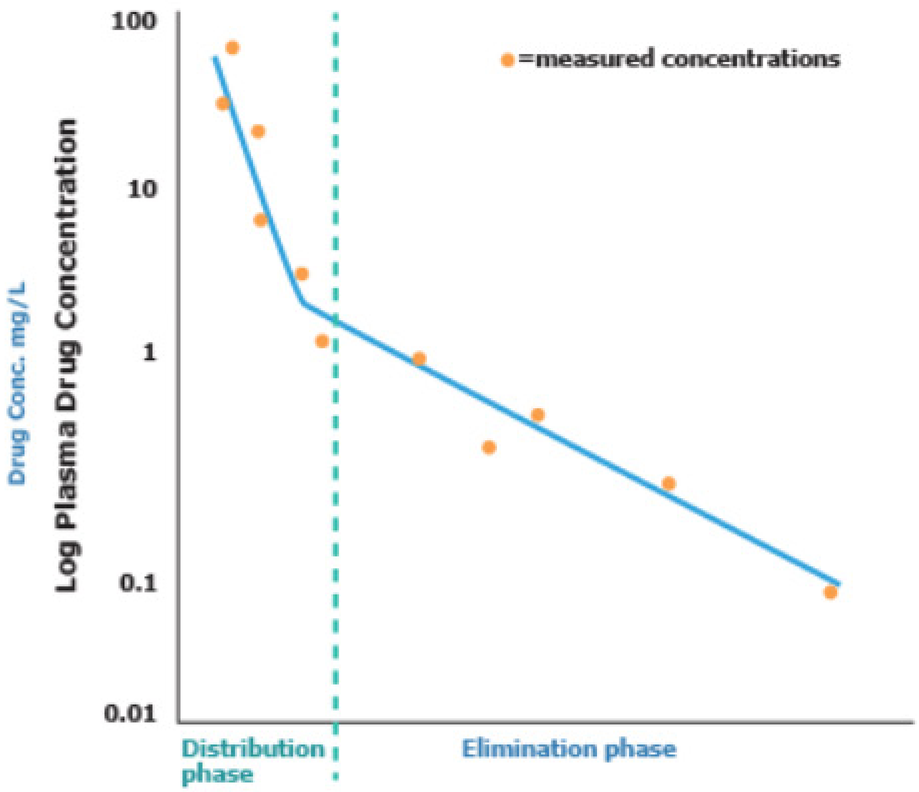

Administration
Absorption and distribution
Elimination
Bile
Portal system
Liver
Metabolites
Kidney
Urine
Oral or rectal
Gut
Feces
Subcutaneous
Skin
Intravenous
Plasma
Breast, sweat glands
Milk, sweat
Intramuscular
Muscle
Brain
Intrathecal
CSF
Placenta
Fetus
Inhalation
Lung
Expired air

▲**Figure 1-3.7A** Elimination

3.7.1 Plasma Versus Time Curve

Drug elimination is often presented graphically as a semilogarithmic plot of drug plasma concentration versus time. In this type of curve, also called log-linear plot (y-axis logarithmic, x-axis linear), the initial steep drop in plasma concentration is due to distribution out of the blood to tissues (the "distribution phase"). After a period of time, the curve shifts to a more gradual drop that is due mostly to elimination of the drug.

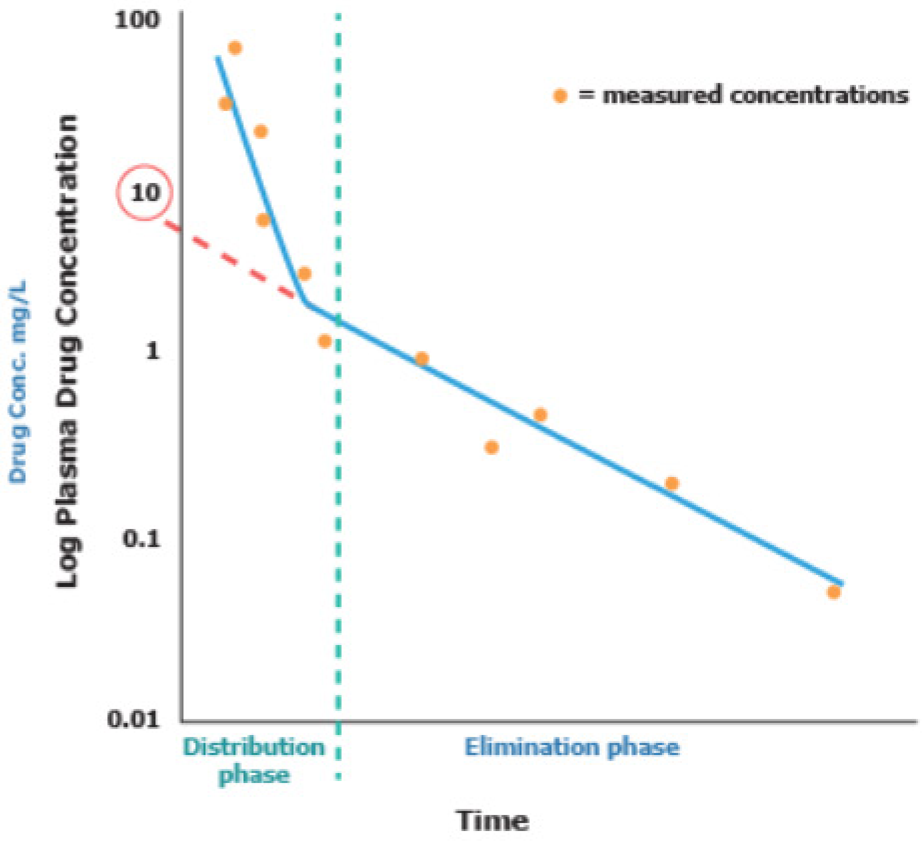
Estimation of Concentration at Time Zero (C_0) Recall that the volume of distribution (V_d) is calculated by the equation V_d=dose/C_0. C_0 is estimated from the place on the y-axis where the elimination phase is extrapolated to intersect. This can be thought of as the hypothetical plasma concentration that would result if a drug were injected and distributed instantaneously.



▶ **Figure 1-3.7B** Plasma Concentration vs. Time Analysis

For the pharmacokinetic data in Figure 1–3.7B, calculate the V_d assuming 200 mg of the drug was injected (concentration units are mg/L). *Extrapolating back to time zero gives an estimate of the hypothetical drug concentration* if distribution had been achieved instantly.

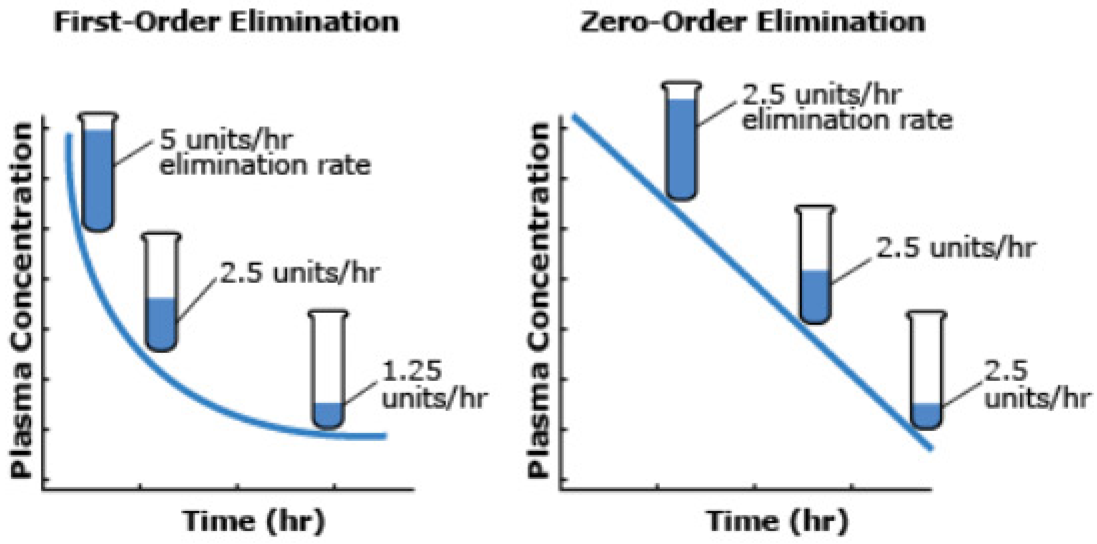
V_d = dose/C_0
= 200 mg/10 mg/L
= 20L



▲ **Figure 1-3.7C** Estimation of Concentration at Time Zero (C0)

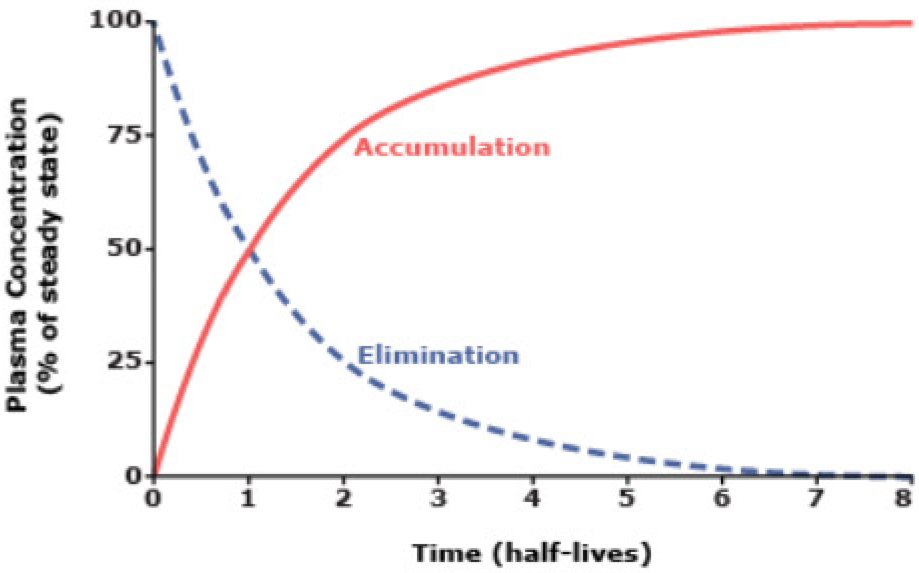
3.7.2 First- vs. Zero-Order Elimination

Most drugs show *first-order (exponential) elimination*. For Step 1, it is important to know a small number of drugs that show the less common *zero-order elimination* (see below).



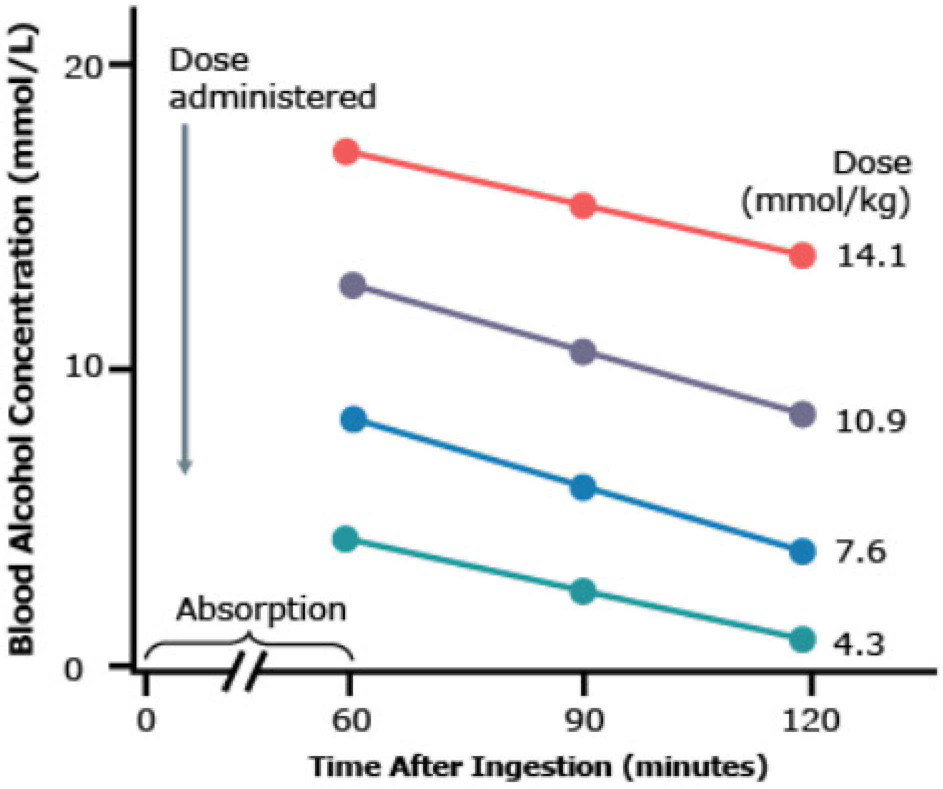
▲**Figure 1-3.7D** First-Order vs. Zero-Order Elimination

First-Order Elimination On a linear-linear plot, this is seen as an exponential drop in plasma concentration over time. On a log-linear plot, this would be a linear drop in plasma concentration. Drugs with first-order elimination have predictable rises and falls in plasma concentration.

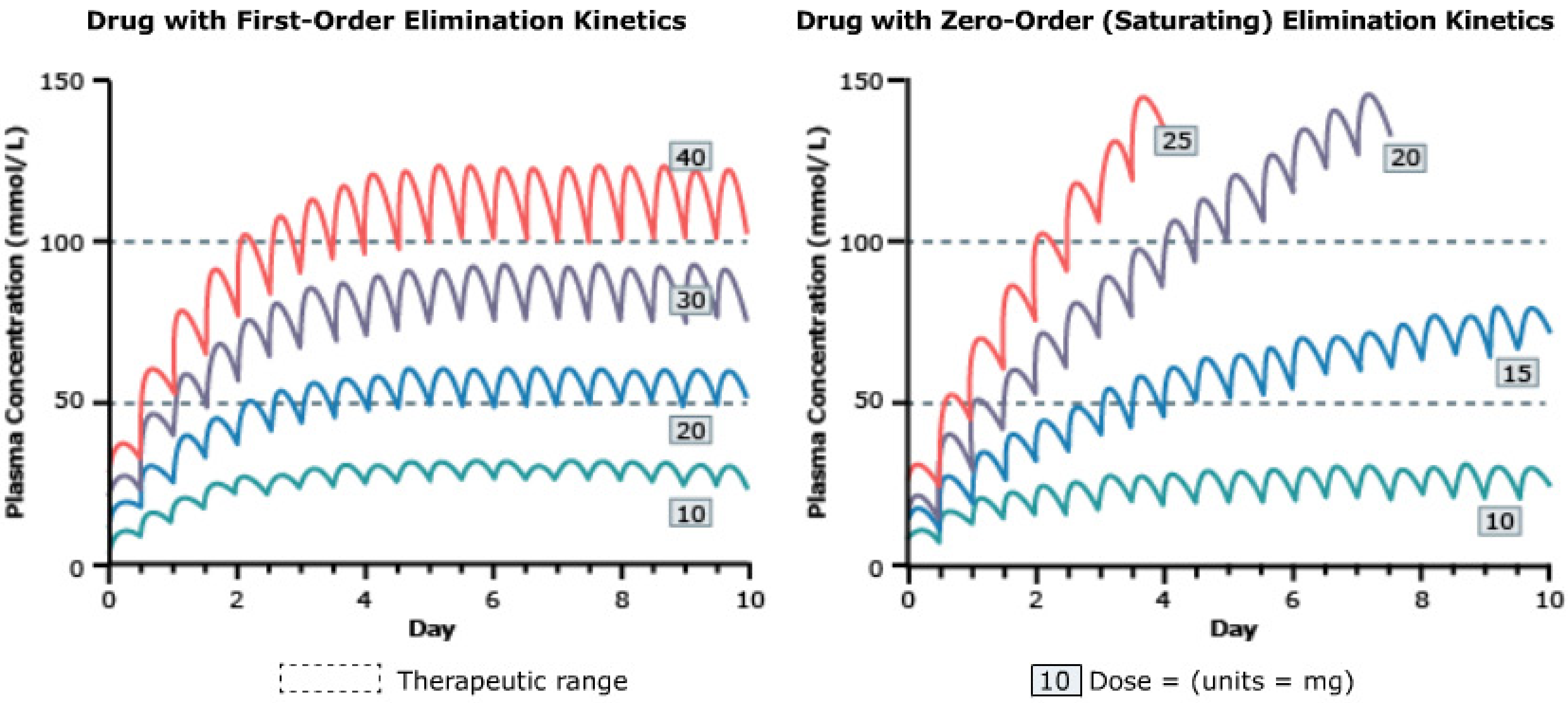


▲**Figure 1-3.7E** Accumulation and Elimination of Drugs Showing First-Order Elimination

Zero-Order Elimination Zero-order elimination occurs at a constant rate and is independent of drug dose and concentration. This typically occurs when the enzyme metabolizing a drug is *saturated* and has already reached a maximal rate of metabolism. On a linear-linear plot of plasma drug concentration, the drop in plasma concentration is slow and linear. Ethanol, aspirin (salicylate), and phenytoin are three drugs that show zero-order elimination at typical doses (or amounts of ingestion for ethanol). Clinically, zero-order drugs have no fixed half-life and can be difficult to dose and manage. This is especially challenging for phenytoin, as this drug is used widely for epilepsy.



▲**Figure 1-3.7F** Zero-Order Elimination



▲**Figure 1-3.7G** Drugs with First-Order and Zero-Order Kinetics

3.7.3 Elimination Half-Life

Half-life ($t_{½}$) is the time needed to eliminate 50% of a drug or, alternatively, to decrease plasma level to 50% of a former level. Half-life can be calculated for drugs with first-order rates of elimination but not for drugs with zero-order elimination. It is high-yield for Step 1 to be able to answer basic problems that involve half-life.

$$t_{1/2} = \frac{V_d \times 0.693}{CL}$$

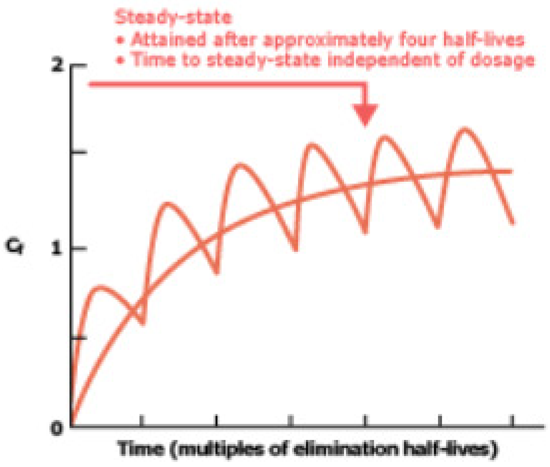
3.7.4 Clearance

Clearance is the rate at which a drug is removed (cleared) from the blood. It is a way of representing drug elimination. Clearance is given in units of volume (of blood) over time (mL/min or L/hr). An important equation is:

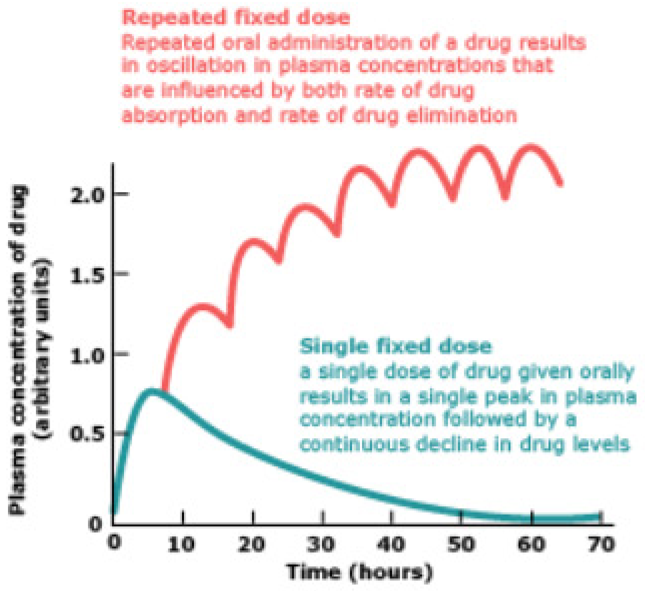
$$CL = \frac{V_d \times 0.693}{t_{1/2}}$$

3.7.5 Steady-State

Steady-state is reached when the amount of drug being administered equals the amount being eliminated. If the drug is being given by continuous intravenous infusion, steady-state is seen as a plateau in drug plasma concentration. If the drug is being dosed at intervals (for example, orally every 12 hours), steady-state is reached when the average plasma concentration stops increasing. Clinically, *steady-state is reached after approximately four half-lives.*

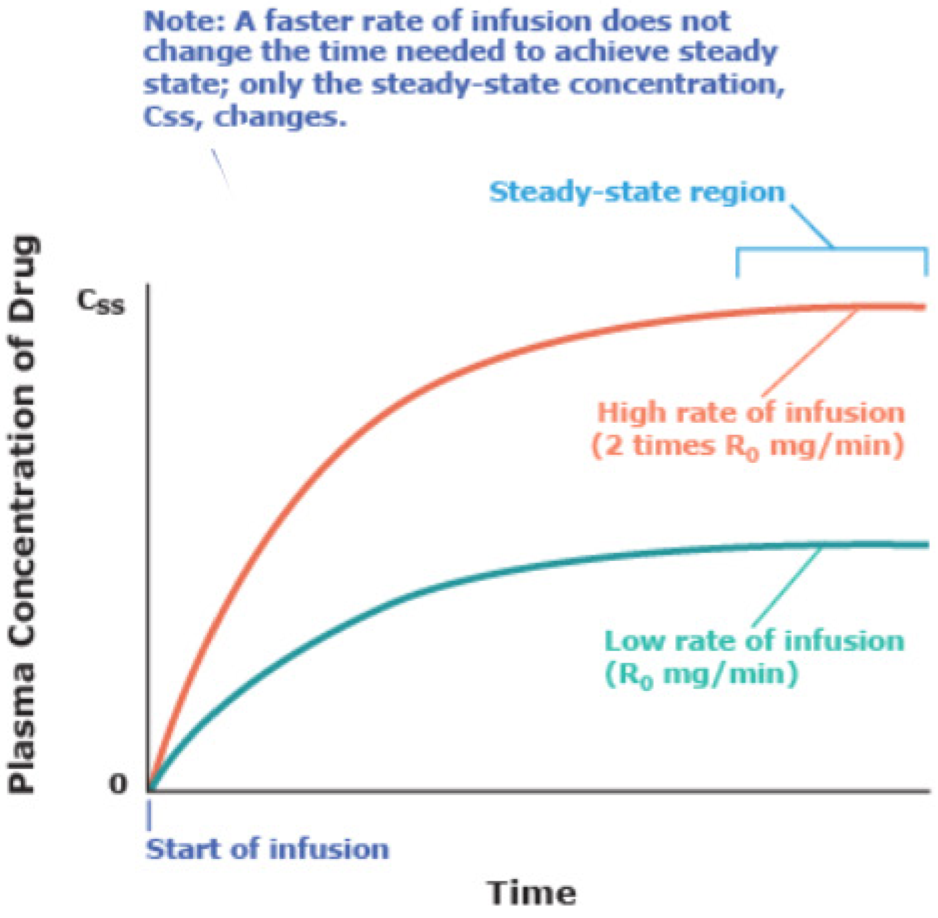


▲ **Figure 1-3.7H** First-Order Elimination Kinetics



▲ **Figure 1-3.7I** Repeated Fixed Dose vs. Single Fixed Dose

Rate of Infusion For continuous intravenous infusions, changing the amount of drug infusion (for example, from 1 mg/min to 2 mg/min) will change the plasma concentration reached at steady-state, but will not change how quickly steady-state is reached.



▲**Figure 1-3.7J** Rate of Infusion

Loading Dose In some cases, it is important to quickly reach therapeutic drug concentrations. This can be achieved with a loading dose, whereby a large dose of drug is given. This does not allow a patient to reach steady-state faster but does speed the rate at which therapeutic concentrations can be achieved. Loading dose can be calculated if V_d and desired plasma concentrations (C_p) are known:

Loading dose = $V_d \times C_p$ [for intravenous dosing]

Loading dose = $(V_d \times C_p)/F$ [for oral administration, with F = bioavailability]

This is one of the few pharmacology equations worth knowing for Step 1.

Consider the following example:

A patient is admitted to the hospital for pneumonia due to *Pseudomonas aeruginosa*. The antibiotic ciprofloxacin is ordered. The CL and V_d of ciprofloxacin are 80 mL/min and 40 L, respectively. If you wish to give an IV loading dose to achieve the therapeutic plasma concentration of 4 mg/L rapidly, how much ciprofloxacin should be given?

$$\begin{aligned}\text{Loading dose} &= V_d \times C_p \\ &= 40\ \text{L} \times 4\text{mg/L} \\ &= 160\ \text{mg}\end{aligned}$$

Calculation of Maintenance Dose Maintenance dose is the amount of drug that needs to be administered to maintain the drug's intended steady-state concentration in the body. It can be calculated with the following equation:

Maintenance dose = $C_{ss} \times$ Clearance
[where C_{ss} is plasma concentration at steady-state]

Consider the following example:

For the same *Pseudomonas aeruginosa* patient administered ciprofloxacin mentioned directly above, what maintenance dose should be administered intravenously every 6 hours to obtain average steady-state plasma concentrations of 4 mg/L?

Rate in = Rate out at steady state
Maintenance dose = $C_{pss} \times$ CL/Bioavailability
Dosage rate = 4 mg/L × (80 mL/min)

Convert mL to L
Dosage rate = 4 mg/L × (0.08 L/min)
Dosage rate = 0.32 mg/min

Calculate amount for every six hours
= 0.32 mg/min × 6 hrs × 60 min/hr
= 115 mg

4 Pharmacodynamics

Pharmacodynamics is the study of the physiological and biochemical effect of drugs after they reach their intended target within the body. Subjects of emphasis in Step 1 include affinity, potency, efficacy, agonism and antagonism, and therapeutic and toxic effects.

4.1 Affinity

Affinity is a measure of how tightly a drug binds to its target receptor. It is summarized by K_d (dissociation constant), which is the concentration of drug at which 50% of receptors are bound to drug. Generally, the lower the K_d, the greater the affinity.

4.2 Potency

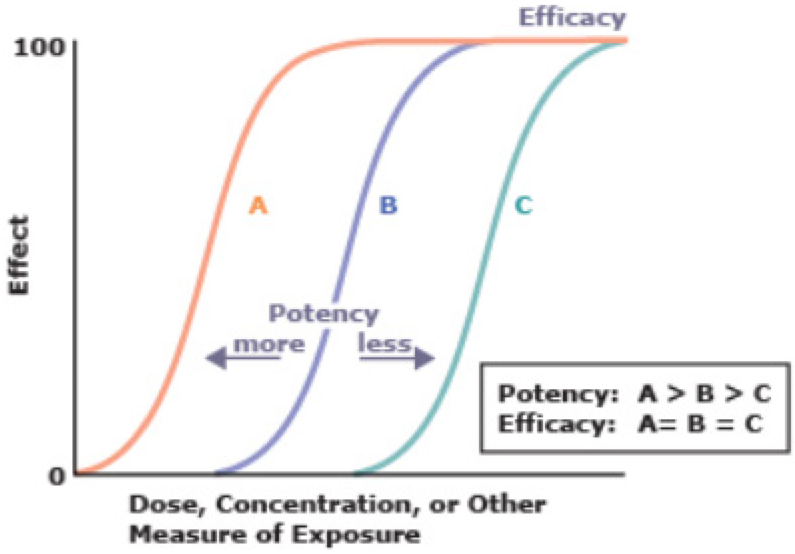
Potency is how much of a drug is required to achieve a desired effect. For example, is a small pill or a larger pill needed to achieve the clinical target? Potency is usually summarized by the following synonymous terms:

- EC_{50} (effective concentration 50%): Concentration required to achieve 50% of drug's maximal effect.
- ED_{50} (effective dose 50%): Dose required to achieve 50% of drug's maximal effect.

A lower EC_{50} or ED_{50} denotes a more potent medication.

4.3 Efficacy

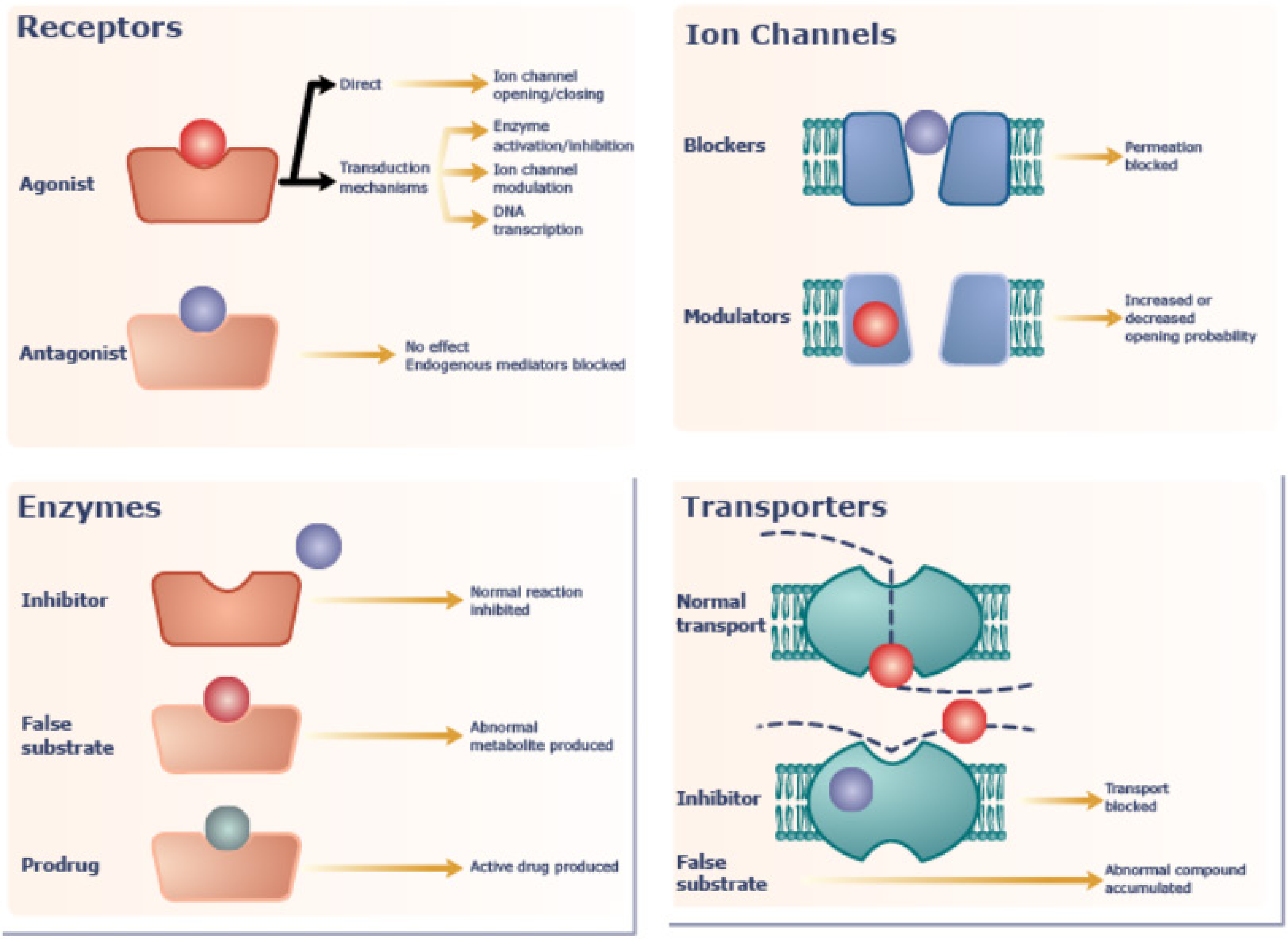
Efficacy is a measure of the maximal effect a drug can achieve. It is not to be confused with potency. Efficacy is not related to dose—it simply describes the *maximal effect achievable regardless of how much drug is needed to achieve that effect*.



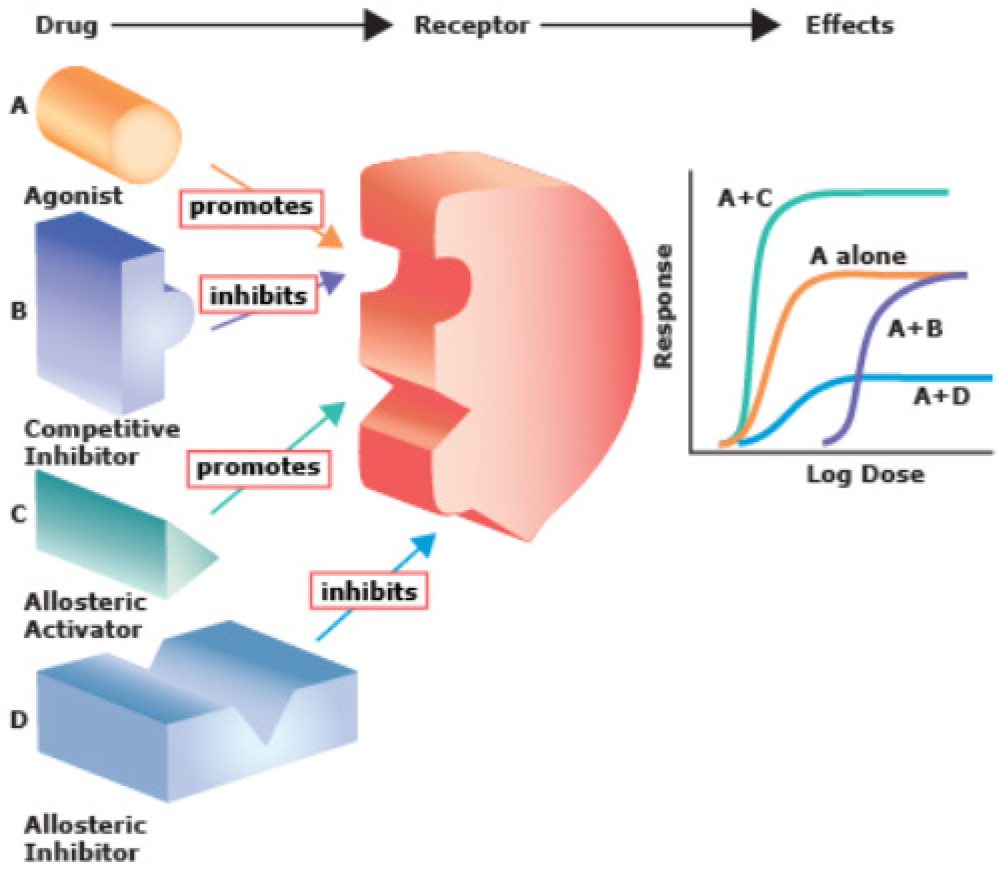
▲ **Figure 1-4.3** Potency and Efficacy

4.4 Agonism and Antagonism

Agonists are drugs that bind to and activate a receptor. A drug may be chemically similar to or even identical to the natural ligands of a receptor. For example, epinephrine and norepinephrine are both endogenous neurotransmitters and are also used clinically as drugs (as with critically ill patients).


Receptors
Agonist
Direct
Ion channel opening/closing
Transduction mechanisms
Enzyme activation/inhibition
Ion channel modulation
DNA transcription
Antagonist
No effect
Endogenous mediators blocked
Ion Channels
Blockers
Permeation blocked
Modulators
Increased or decreased opening probability
Enzymes
Inhibitor
Normal reaction inhibited
False substrate
Abnormal metabolite produced
Prodrug
Active drug produced
Transporters
Normal transport
Inhibitor
Transport blocked
False substrate
Abnormal compound accumulated

▲Figure 1-4.4A Receptors, Ion Channels, Enzymes, and Transporters


Drug
Receptor
Effects
A
Agonist
promotes
B
inhibits
Competitive Inhibitor
promotes
C
Allosteric Activator
inhibits
D
Allosteric Inhibitor
Response
Log Dose
A+C
A alone
A+B
A+D

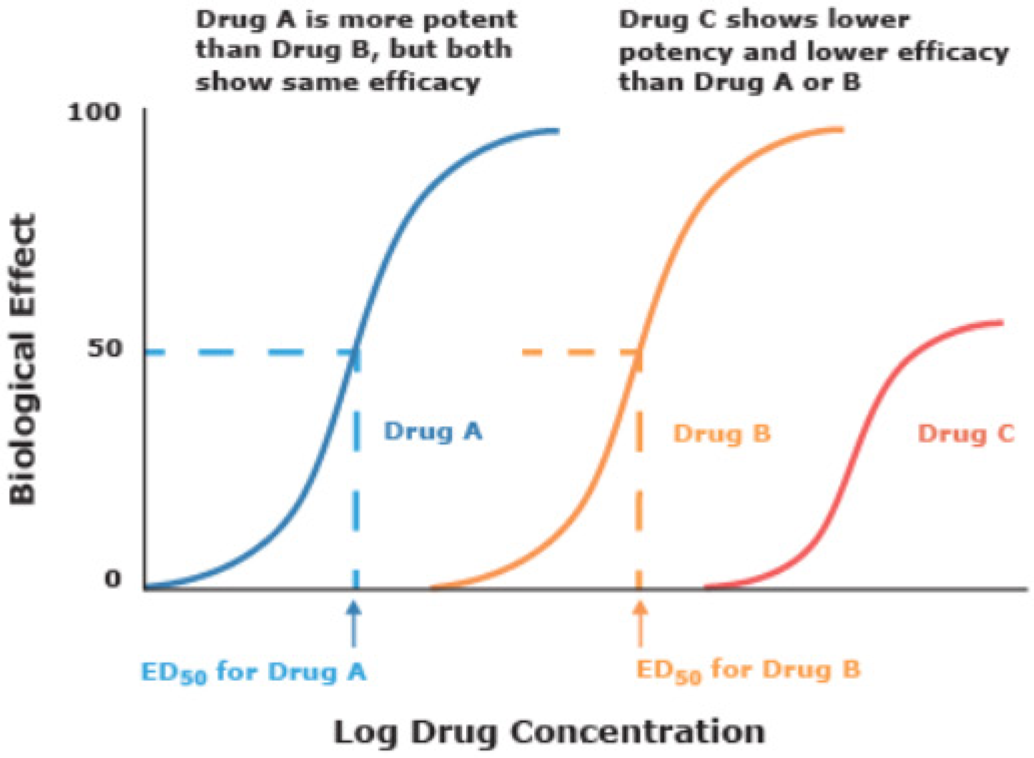
▲Figure 1-4.4B Activators and Inhibitors

4.4.1 Full Agonists

Full agonists produce the maximal response (efficacy) at the receptor. Examples include morphine (μ-opioid receptor) and dobutamine (β1-adrenergic receptor).

4.4.2 Partial Agonists

Partial agonists bind to the same receptor site as full agonists but elicit a smaller maximal effect. In other words, partial agonists have lower efficacy than full agonists. Partial agonists may have lower, equal, or higher potency than full agonists. One clinical application of partial agonists is to have a dual agonist-antagonist role. For example, buprenorphine (Suboxone) is a partial agonist at the μ-opioid receptor used to treat opiate addiction. In patients taking a full agonist (like morphine or heroin) and buprenorphine, the lower efficacy of the buprenorphine reduces the clinical effects of the full agonist. However, when taken by itself, buprenorphine has weak opiate effects and lessens the withdrawal symptoms in someone recovering from opiate addiction.

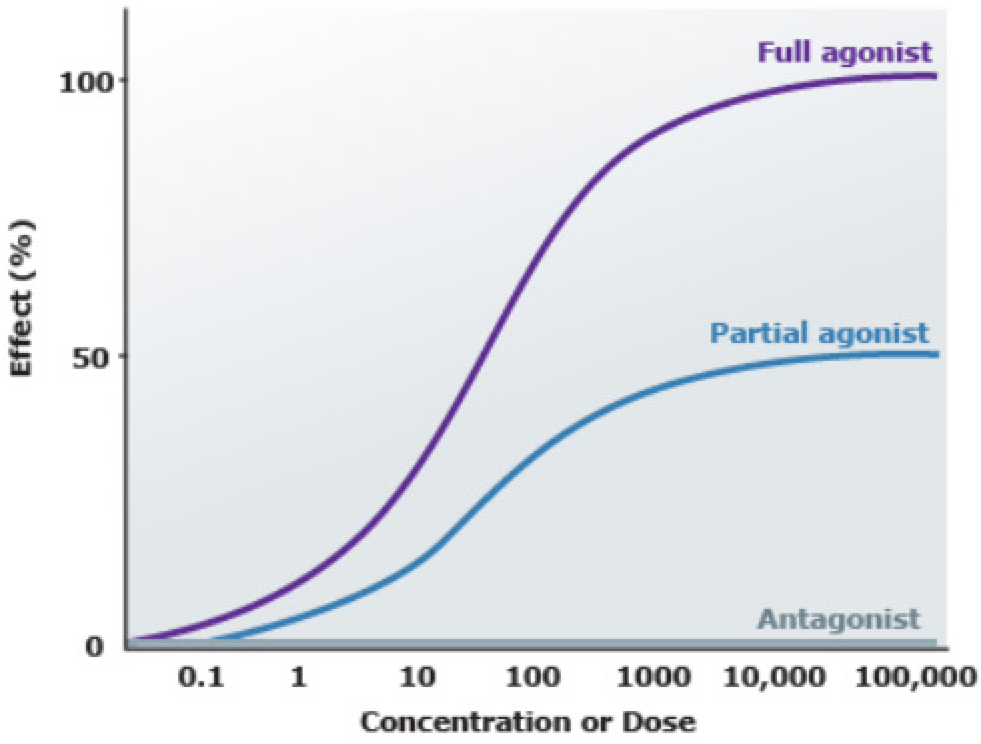


▲**Figure 1-4.4C** Partial Agonists

4.4.3 Antagonists

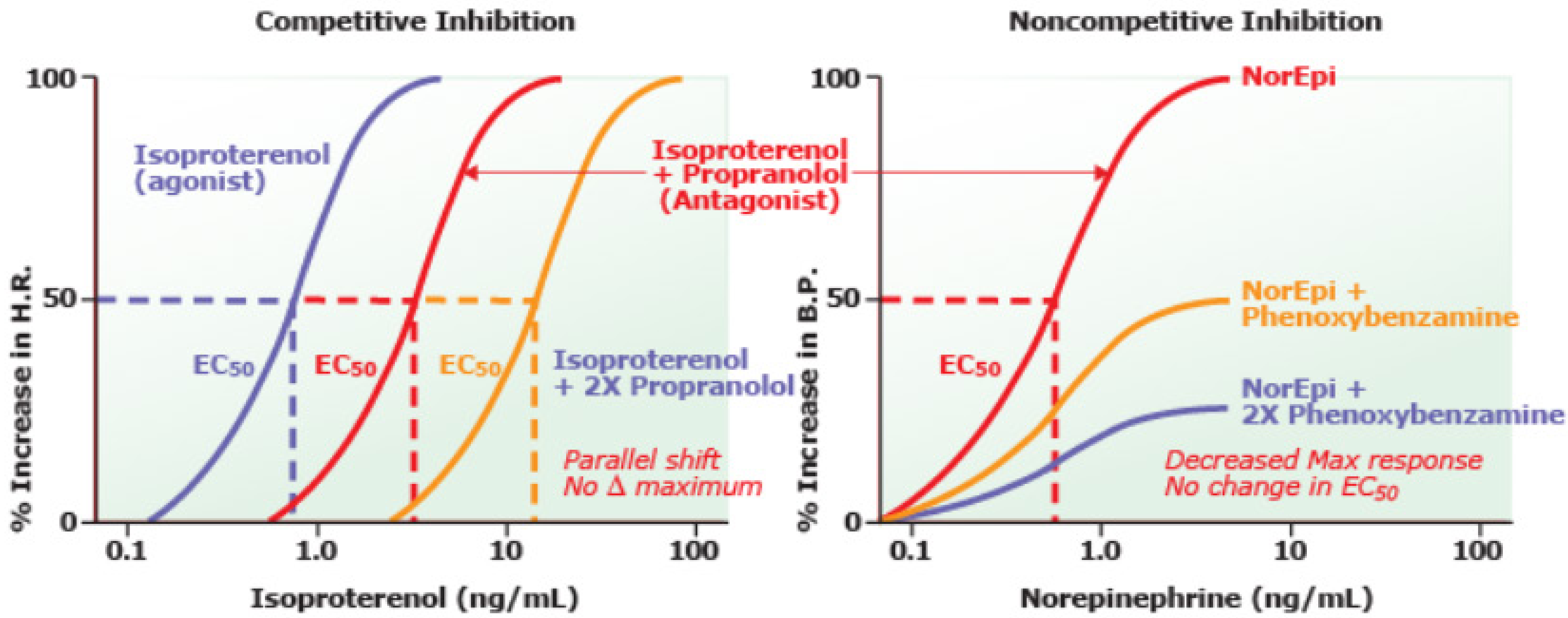
Antagonists block the effect of agonists. By definition, *a true antagonist has no efficacy on its own*. Types of antagonism include competitive, noncompetitive, irreversible, chemical, and physiologic.

Competitive Antagonism Competitive antagonists compete with agonists for the same binding site on the receptor. The hallmark of competitive antagonism is *the effects of the antagonist can be completely reversed by giving high doses of the agonist* (if clinically feasible). There are many examples of competitive antagonists including atropine (muscarinic acetylcholine receptor), propranolol (β-adrenergic receptors), and naloxone (μ-opioid receptor).



▲**Figure 1-4.4D** Full Agonist, Partial Agonist, and Antagonist

Noncompetitive Antagonism Noncompetitive antagonists bind to a different site on the target receptor than the agonist. They are also called "allosteric inhibitors." An analogy can be to a lock on the door. A competitive antagonist blocks the key from entering the lock. Noncompetitive antagonists decrease the efficacy of the agonist. A key difference between competitive and noncompetitive antagonists is that *noncompetitive cannot be overcome simply with more of the agonist*. There are a few examples of clinically important drugs that are noncompetitive antagonists. Ketamine (dissociative anesthetic) and phencyclidine (PCP, "angel dust") are noncompetitive antagonists of the NMDA glutamate receptor.



▲**Figure 1-4.4E** Agonist, Competitive Antagonist, and Noncompetitive Antagonist

Irreversible Antagonism Irreversible antagonists covalently modify a receptor and permanently inhibit its action. Examples include aspirin (cyclooxygenases 1 and 2; COX-1 and COX-2 inhibitor) and phenoxybenzamine (α- and β-adrenergic receptor antagonist). The effect of these antagonists can be overcome only by synthesis of new receptors. A clinically important example of an irreversible inhibition is aspirin, which interferes with platelet aggregation by irreversibly inhibiting COX-1. Because platelets lack nuclei, the aspirin effect on platelets is overcome only by production of new platelets.

Chemical Antagonism Chemical antagonism does not involve action at the receptor, but instead occurs when a complex is formed between a drug and another compound before the drug can act on the receptor. There are a number of clinical examples:

- Heavy metal chelators (e.g., EDTA or succimer DMSA for lead)
- Deferoxamine for iron
- Protamine for heparin

Physiologic Antagonism Physiologic antagonism is a general term that describes one drug opposing the effect of another drug, where each acts via different receptors. An example is acetylcholine and norepinephrine with respect to heart rate. Acetycholine slows heart rate by activating muscarinic acetylcholine receptors. Norepinephrine raises heart rate by activating β-adrenergic receptors.

4.5 Dose-Response Curves of Therapeutic and Toxic Effects

It can be helpful to compare the dose-response curve for a drug for a therapeutic effect (as in lowering blood pressure for an antihypertensive) versus the dose-response for causing a toxic effect (such as dizziness).

4.5.1 Therapeutic Index

The therapeutic index (TI) is the ratio of the dose that causes a toxic effect versus the dose that produces a therapeutic effect. Classically, therapeutic index was defined in animal experiments as the LD_{50} (dose that kills 50% of animals) divided by the ED_{50} for the therapeutic effect.

Important Concept

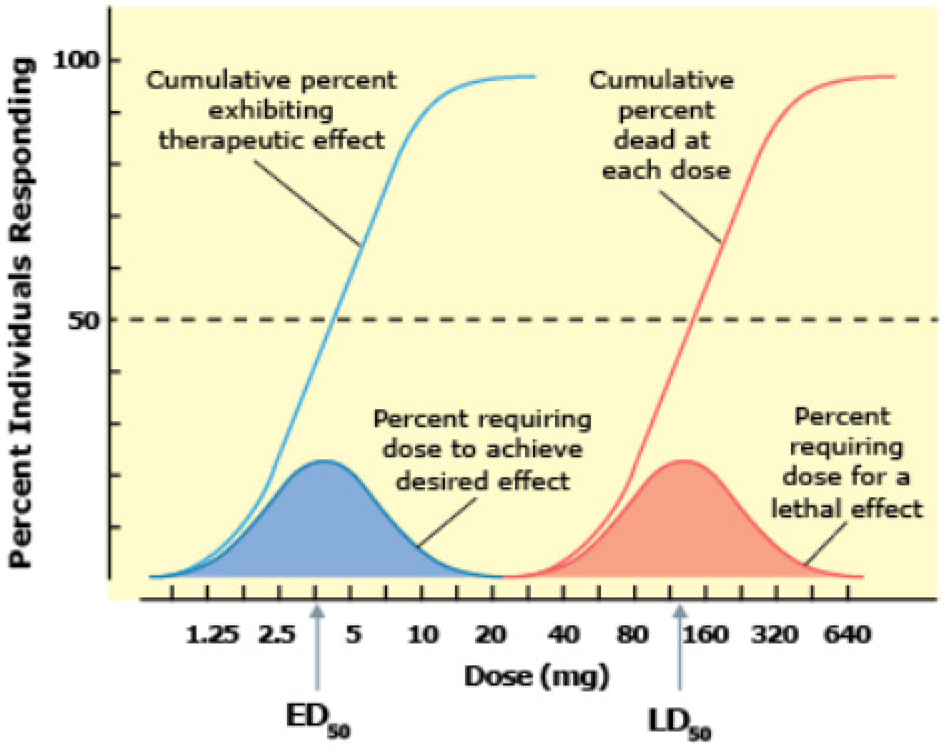
Step 1 questions on therapeutic index can use unusual ratios or display complicated data sets.

$$TI = \frac{LD_{50}}{ED_{50}}$$

This ratio gives an indication of how likely a drug is to produce severe or even lethal side effects. However, in principle, a therapeutic index could be defined as any ratio between a toxic dose and effective dose. For example, a TD_1/ED_{99} ratio would define the amount of separation between a dose that is toxic in 1% of patients versus a dose that is effective in 99% of patients.

Drugs With Low Therapeutic Index There is a group of drugs classically referred to as *low therapeutic index*. These include lithium, warfarin, phenytoin, aminoglycoside antibiotics, cancer chemotherapy agents, thyroid medications, and general anesthetics. For some of these drugs, therapeutic drug monitoring of drug plasma levels is followed to maintain therapeutic effect while minimizing toxic side effects.

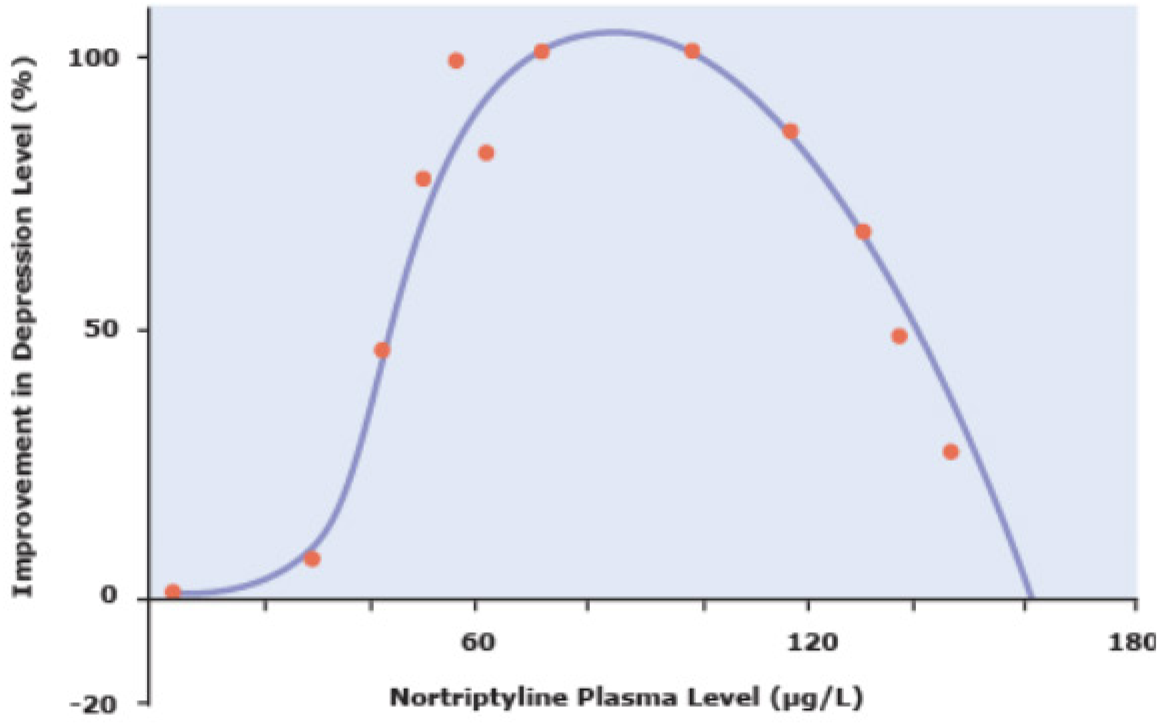
Drugs With High Therapeutic Index There are many drugs with high therapeutic index. Some previously required prescriptions but are now available over-the-counter. Examples include histamine-2 receptor antagonists (e.g., ranitidine) and proton pump inhibitors (e.g., omeprazole).



▲**Figure 1-4.5A** Dose-Response Plots

4.5.2 Unusual Dose-Response Curves

In clinical practice, some drugs exhibit unusual dose-response curves. An example is the "inverted U-shaped" curve of nortriptyline dose versus therapeutic response for treating major depression. In this case, higher doses of nortriptyline are actually less effective than lower doses, and a target plasma level of approximately 100 µg/L would be optimal.



▲**Figure 1-4.5B** Nortriptyline Dose-Response

5 Federal Oversight of Pharmaceuticals

The Food and Drug Administration (FDA) is the primary federal agency overseeing drug approval and marketing. The Drug Enforcement Agency (DEA) regulates and enforces laws related to controlled substances.

5.1 Drug Development and the Food and Drug Administration (FDA)

The FDA closely regulates the safety and efficacy of drugs in the United States. This includes determining what indications a drug is approved for and how the drug is marketed. The FDA has more limited oversight for compounds classified as nutritional supplements and herbal remedies. These compounds do not require the rigorous approval process for prescription medications and may be removed from the market only if clear evidence of harm is proven (as occurred with ephedrine).

Multiple steps are involved in the development and approval of a new drug.

5.1.1 Preclinical Studies

Preclinical (before human testing) studies include laboratory experiments and animal studies. These provide the basis for testing a potential new drug in humans.

5.1.2 Phase 1 Trials

Phase 1 trials ask the basic question of "Is the drug safe?" and typically involve healthy volunteers. Exceptions are trials of drugs with potential high toxicity such as cancer chemotherapy, where the trials are in patients with end-stage cancer. Phase 1 studies work out toxicity and pharmacokinetics of the drug.

5.1.3 Phase 2 Trials

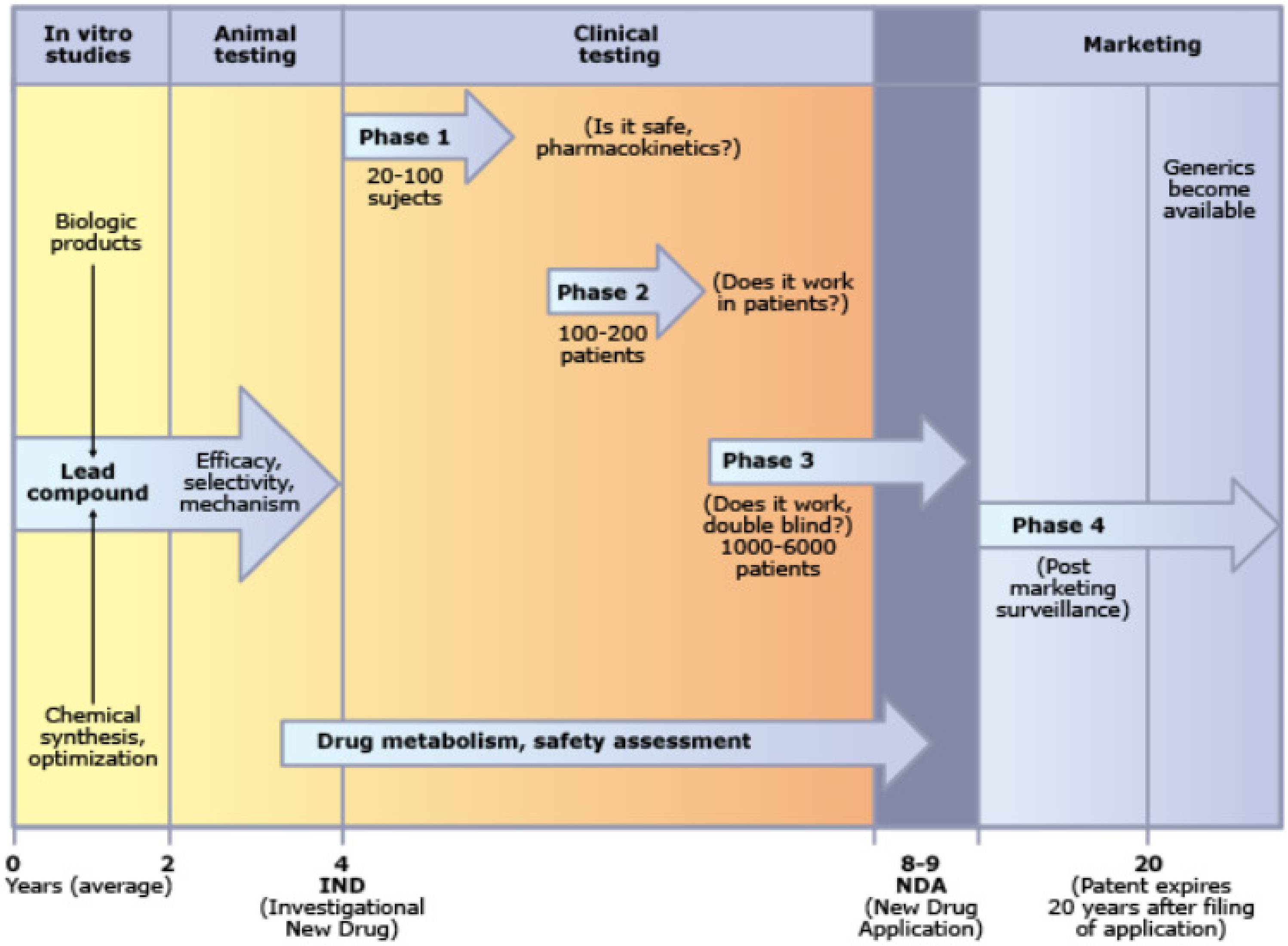
Phase 2 trials are usually the first test of a drug in a population with disease, except drugs such as cancer chemotherapy, as described above. Phase 2 trials ask, "Does the drug work?" by determining the drug's effectiveness in treating a group of patients with disease.

5.1.4 Phase 3 Trials

If phase 2 trials go well, a drug can proceed to phase 3 trials, which ask, "How well does the drug work, and what are the most common side effects?" Phase 3 trials are often randomized (patients randomly assigned to treatment or placebo) and double-blind (neither physician nor patient knows what the patient is getting). Phase 3 is usually the largest and most expensive phase of clinical trials.

5.1.5 Phase 4 Trials

Phase 4 trials are post-marketing surveillance studies and are not required for every drug. These may be requested by the FDA to look for suspected adverse effects. For instance, a drug may have caused liver enzyme elevations (such as alanine aminotransferase) in some patients in earlier trials, and the FDA wants the pharmaceutical company to monitor for liver toxicity even after the drug is approved for marketing.


In vitro studies
Animal testing
Clinical testing
Marketing
Phase 1
20-100 sujects
(Is it safe, pharmacokinetics?)
Biologic products
Phase 2
100-200 patients
(Does it work in patients?)
Generics become available
Lead compound
Efficacy, selectivity, mechanism
Phase 3
(Does it work, double blind?) 1000-6000 patients
Phase 4
(Post marketing surveillance)
Chemical synthesis, optimization
Drug metabolism, safety assessment
0
Years (average)
2
4
IND
(Investigational New Drug)
8-9
NDA
(New Drug Application)
20
(Patent expires 20 years after filing of application)

▲**Figure 1-5.1** Drug Development and Testing

5.2 Controlled Substances and the Drug Enforcement Agency (DEA)

Certain drugs are designated as controlled substances and regulated tightly because of their potential for being abused (*abuse liability*) and causing harm. The DEA oversees the use of controlled substances. In the United States, controlled substances are in five categories:

5.2.1 Schedule I Drugs

Schedule I drugs are considered to have such a high abuse liability and low medical utility that they are banned from medical use in the United States, being available only for highly restricted research studies. Examples include heroin, marijuana (except in certain states), lysergic acid diethylamide (LSD), methcathinone ('kat'), phencyclidine (PCP), mescaline, peyote, and methaqualone. Note that some of these drugs are legally available in other parts of the world.

5.2.2 Schedule II Drugs

Schedule II drugs have a high potential for abuse but can be prescribed under restricted conditions, such as triplicate prescriptions and no automatic refills. This category contains opiates, amphetamines, and some short-acting sedatives. Specific examples include morphine, oxycodone, cocaine, meperidine, secobarbital, amphetamine, methamphetamine, and methylphenidate.

5.2.3 Schedule III Drugs

Schedule III drugs are considered lower risk than Schedule II. Examples include anabolic steroids (e.g., clostebol, methyltestosterone, stanozolol), the marijuana derivative dronabinol, and hydrocodone/acetaminophen.

5.2.4 Schedule IV Drugs

Schedule IV drugs are considered to have low potential for abuse but can have limited physical and/or psychic dependence. Examples include alprazolam, clonazepam, lorazepam, and phenobarbital.

5.2.5 Schedule V Drugs

Schedule V drugs have low abuse potential and can even be sold in some states without a prescription. Examples include pregabalin and cough medications with low doses of codeine.

▼**Table 1-5.2** Classification of Controlled Substances

Schedule	Potential for Abuse	Other Comments
I	Very high	No accepted medical use. Lack of accepted safety as drug.
II	High	Current accepted medical use. Abuse may lead to psychological or physical dependence.
III	Less than I or II	Current accepted medical use. Moderate or low potential for physical dependence and high potential for psychological dependence.
IV	Less than III	Current accepted medical use. Limited potential for dependence.
V	Less than IV	Current accepted medical use. Limited dependence possible.

Katsung, Bertram et al, *Basic and Clinical Pharmacology*, 12th ed. © 2012 The McGraw-Hill Companies, Inc.

CHAPTER 2 Autonomic Pharmacology

1 Autonomic Receptors and Their Distributions

The autonomic nervous system regulates a variety of physiologic processes, including pupillary dilation/contraction, salivation, heart rate, digestion, and voiding. This autonomic nervous system has two subsystems:

- **Sympathetic nervous system:** Controlled by the thoracic and lumbar ("thoracolumbar") sections of the spinal cord, this system mediates "fight-or-flight" type of responses (increased heart rate, pupillary dilation, reduced gastrointestinal peristalsis).
- **Parasympathetic nervous system:** Regulated via cranial nerves and the sacral section of the spinal cord ("craniosacral"), this system mediates "rest-and-digest" functions (increased salivation, increased intestinal peristalsis, and decreased heart rate).

1.1 Adrenergic and Cholinergic Neurotransmitters

Receptors for adrenergic and cholinergic neurotransmitters are found at autonomic ganglia and in end organs/tissues. Adrenergic neurons release norepinephrine. Adrenergic receptors (adrenoreceptors) may be activated by norepinephrine or epinephrine. Cholinergic neurons release acetylcholine (ACh).

1.2 Acetylcholine Biosynthesis and Breakdown

ACh is synthesized from choline and acetyl CoA by the enzyme choline acetyltransferase. ACh is broken down by the enzyme acetylcholinesterase (AChE) into choline and acetate.

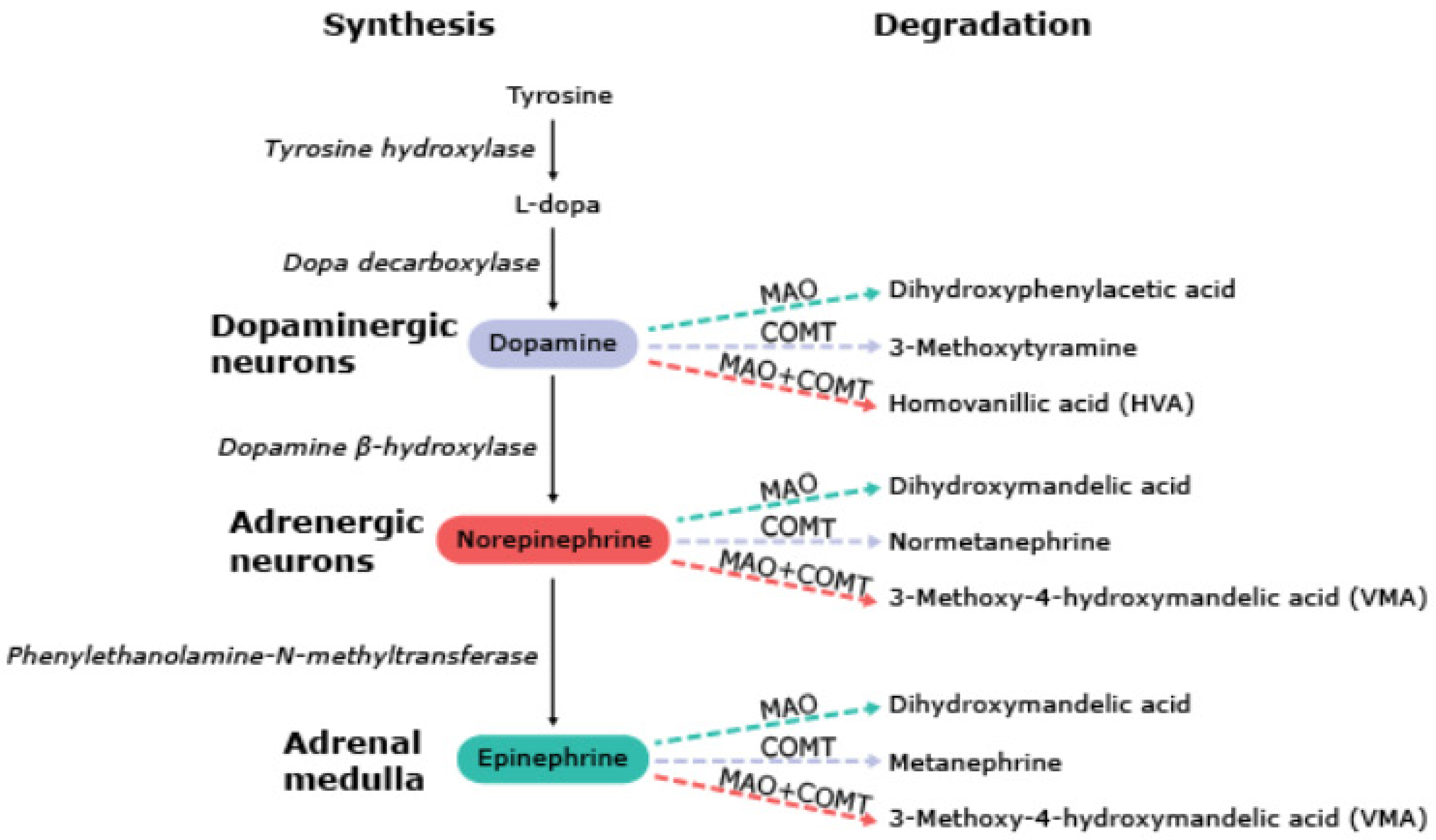
1.3 Catecholamine Biosynthesis and Breakdown

The catecholamines (dopamine, norepinephrine, and epinephrine) are synthesized from the amino acid tyrosine. The rate-limiting step is the conversion of tyrosine to *L*-dopa by tyrosine hydroxylase. Epinephrine is synthesized in the adrenal medulla, which produces the enzyme phenylethanolamine-*N*-methyltransferase. The primary enzymes that break down catecholamines are monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT).

USMLE™ Key Concepts

For Step 1, you must be able to:

- Describe the anatomic distribution and physiologic functions of cholinergic and adrenergic receptors in the sympathetic and parasympathetic nervous systems.
- Identify agonist and antagonist drugs of the major cholinergic and adrenergic receptors, and the clinical applications of these drugs.
- Explain the synthetic pathway for prostaglandin, leukotrienes, and prostacyclin and the drugs that affect this system.
- Describe the mechanism of action, clinical uses, and adverse effects of aspirin, ibuprofen, naproxen, indomethacin, COX-2 inhibitors, and acetaminophen.


Synthesis
Degradation
Tyrosine
Tyrosine hydroxylase
L-dopa
Dopa decarboxylase
Dopaminergic neurons
Dopamine
MAO
Dihydroxyphenylacetic acid
COMT
3-Methoxytyramine
MAO+COMT
Homovanillic acid (HVA)
Dopamine β-hydroxylase
Adrenergic neurons
Norepinephrine
MAO
Dihydroxymandelic acid
COMT
Normetanephrine
MAO+COMT
3-Methoxy-4-hydroxymandelic acid (VMA)
Phenylethanolamine-N-methyltransferase
Adrenal medulla
Epinephrine
MAO
Dihydroxymandelic acid
COMT
Metanephrine
MAO+COMT
3-Methoxy-4-hydroxymandelic acid (VMA)

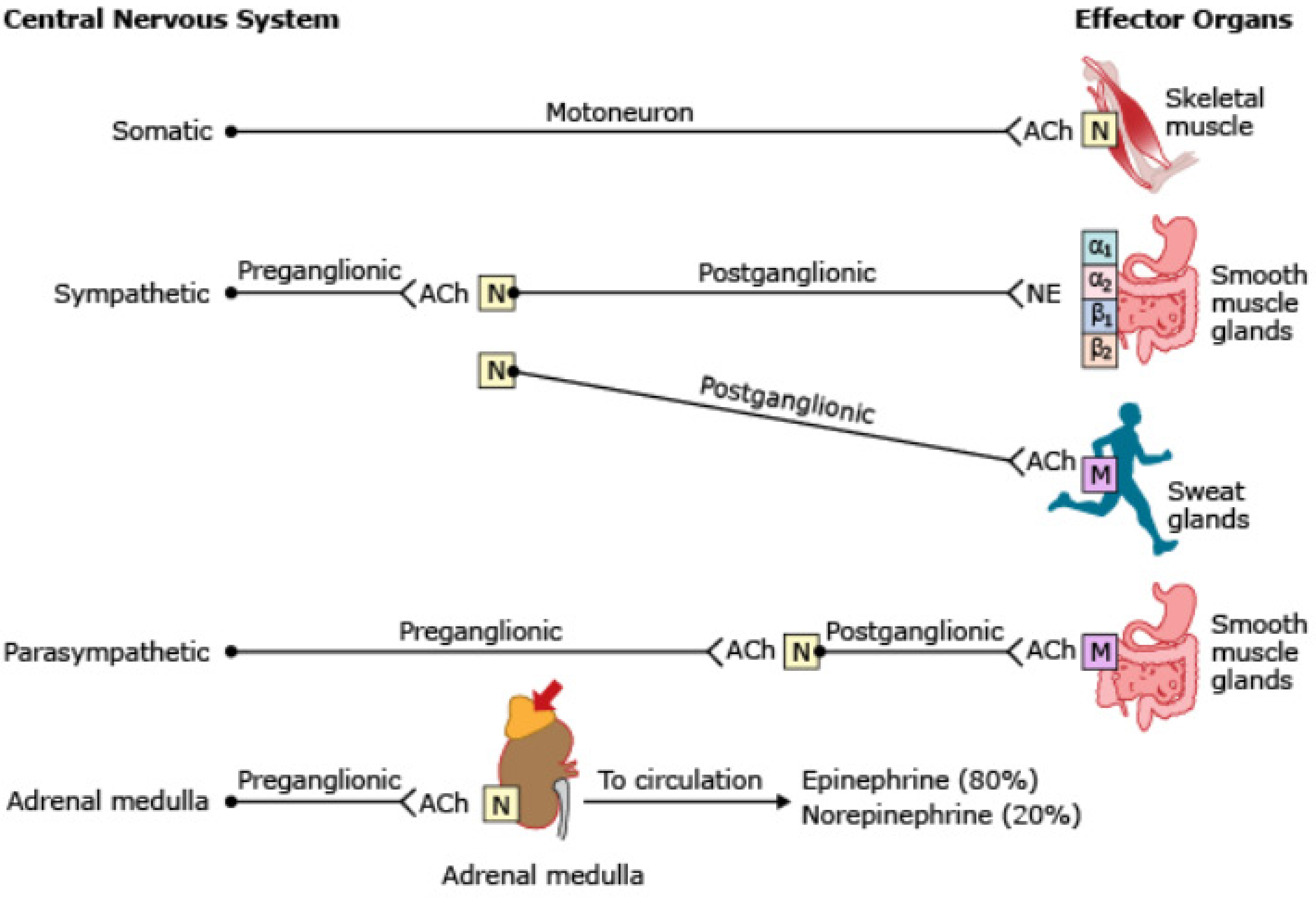
▲ **Figure 2-1.3** Norepinephrine and Epinephrine

1.4 Distributions of Receptors in the Sympathetic Nervous System

Neural transmission for the sympathetic nervous system originates from the thoracolumbar spinal cord. Prior to reaching end organs, the axons synapse on ganglia located near the spinal cord. The receptors in the ganglia are neuronal nicotinic acetylcholine receptors. Axons from neurons in the sympathetic ganglia tend to be long as they must travel some distance to reach end organs/tissues. Most sympathetic synapses in the end organs use adrenergic receptors—some combination of α_1, α_2, β_1, β_2, and/or β_3. An exception is certain sweat glands that use muscarinic acetylcholine receptors despite being part of the sympathetic nervous system.

1.5 Distributions of Receptors in the Parasympathetic Nervous System

Neural transmission for the parasympathetic nervous system originates from the cranial nerves or sacral spinal cord. Parasympathetic ganglia tend to be close to the target organs; therefore, the axons originating from the cranial nerves or sacral neurons are long. As in the sympathetic nervous system, the parasympathetic ganglia use neuronal nicotinic acetylcholine receptors. Parasympathetic synapses in the target organs use muscarinic acetylcholine receptors—some combination of M_1 to M_5 receptors.


Central Nervous System
Effector Organs
Somatic
Motoneuron
ACh
N
Skeletal muscle
Sympathetic
Preganglionic
ACh
N
Postganglionic
NE
α1
α2
β1
β2
Smooth muscle glands
N
Postganglionic
ACh
M
Sweat glands
Parasympathetic
Preganglionic
ACh
N
Postganglionic
ACh
M
Smooth muscle glands
Adrenal medulla
Preganglionic
ACh
N
To circulation
Epinephrine (80%)
Norepinephrine (20%)
Adrenal medulla

▲**Figure 2-1.5** Neural Transmission

2

Acetylcholine (Cholinergic) Receptors

Cholinergic receptors are divided into muscarinic and nicotinic receptors. These receptors receive their name from the natural compounds they bind in addition to the endogenous agonist acetylcholine (ACh).

2.1 Muscarinic Acetylcholine Receptors

Muscarine is an alkaloid derived from mushrooms, such as the deadly *Clitocybe dealbata*, and it is the prototypical selective agonist for muscarinic receptors. Muscarinic receptors are divided into five subtypes, M_1 to M_5, with the following broad functions:

- M_1: Neural
- M_2: Cardiac
- M_3: Glandular/smooth muscle
- M_4: Inhibitory regulation of striatum
- M_5: Unclear role in vivo

The odd-numbered (M_1, M_3, and M_5) muscarinic receptors act by way of the inositol triphosphase (IP_3) pathway. These three receptors mediate parasympathetic vasodilation, bronchoconstriction, increased GI tract motility, increased salivation, increased sweating, voiding (contraction of detrusor and relaxation of trigone), and defecation.

The even-numbered (M_2 and M_4) muscarinic receptors inhibit adenylyl cyclase and reduce cyclic AMP (cAMP). In the heart, activation of M_2 receptors lead to the opening of K^+ channels and the inhibition of Ca^{2+} channels, slowing heart rate and decreasing contractility.

2.2 Nicotinic Acetylcholine Receptors

Nicotine is derived from the nightshade family of plants, such as tobacco, and it is the prototypical selective agonist for nicotinic receptors. The two main types of nicotinic receptors are muscle and neuronal. The muscle type is found on skeletal muscle and mediates contraction. Neuronal nicotinic receptors are found in autonomic ganglia (both sympathetic and parasympathetic) and also in the brain and adrenal medulla. Drugs may affect muscle or neuronal nicotinic receptors or both.

2.3 Nicotinic Acetylcholine Receptor Agonists

Nicotine from tobacco has prominent actions on neuronal nicotinic receptors, both in the brain (e.g., influencing release of other neurotransmitters) and in autonomic ganglia. Actions on muscle-type nicotinic receptors are minimal for typical tobacco uses. Nicotine may be given orally or transdermally to treat nicotine dependence.

2.3.1 Varenicline

Varenicline is a partial agonist at the $\alpha_4\beta_2$ subtype of the neuronal nicotinic receptor that mediates the "reward effect" of nicotine. Varenicline has been shown to help treat nicotine dependence. Varenicline has an FDA black box warning for causing psychiatric side effects, including suicidality. Varenicline should be avoided by patients with depression or other mood disorders.

2.3.2 Succinylcholine

Succinylcholine is an agonist of muscle-type nicotinic receptors used as a neuromuscular blocker. This drug is discussed in detail in chapter 4.

2.4 Nicotinic Acetylcholine Receptor Antagonists

Antagonists of the muscle-type nicotinic receptors are used as neuromuscular blockers. Examples include atracurium, mivacurium, pancuronium, and vecuronium. These drugs are discussed in detail in chapter 4.

2.5 Muscarinic Acetylcholine Receptor Agonists

Muscarinic receptor agonists are used in the treatment of glaucoma, neurogenic bladder, and xerostomia (dry mouth). Bethanechol, carbachol, and pilocarpine are used topically in the treatment of glaucoma. Bethanechol is used to manage urinary retention in disorders that impair bladder emptying.

Pilocarpine is used to stimulate sweat production for the sweat chloride test for diagnosing cystic fibrosis. Methacholine is used for the "methacholine challenge" for diagnosing hyperreactive bronchioles. This challenge is rarely used.

2.6 Muscarinic Acetylcholine Receptor Antagonists

Many drugs have muscarinic receptor antagonist effects. The prototype selective muscarinic antagonist (antimuscarinic) is atropine. Other drugs with antimuscarinic effects include tricyclic antidepressants, trihexyphenidyl, phenothiazine antipsychotics, and diphenhydramine.

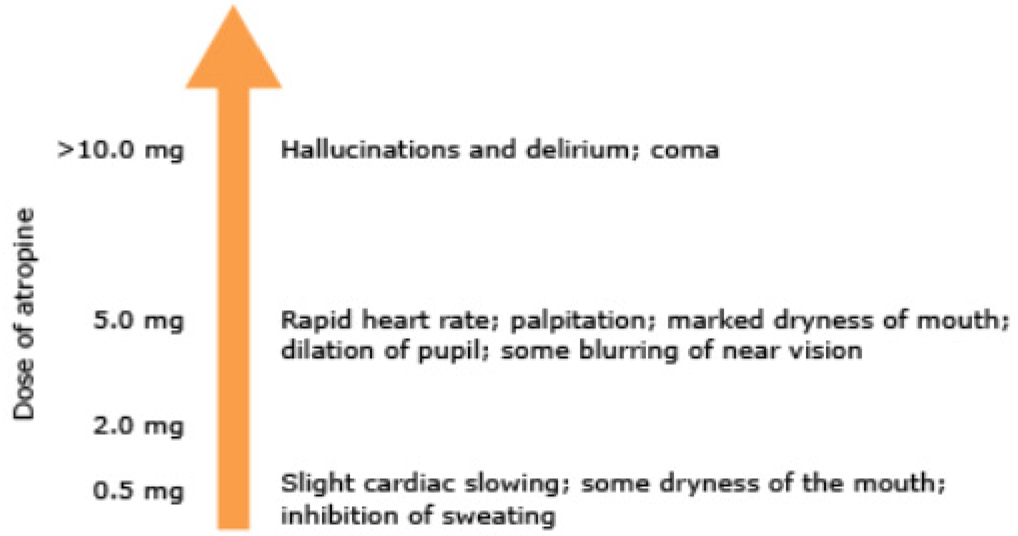
2.6.1 Clinical Applications

Antimuscarinics are used for a number of clinical applications including:

- Severe bradycardia (atropine)
- Acetylcholinesterase poisoning (atropine)
- Asthma and COPD (ipratropium, tiotropium)
- Bladder spasm, urinary incontinence (oxybutynin, tolterodine)
- Motion sickness (scopolamine)
- Dry secretions (glycopyrrolate)
- Parkinsonism, including drug-induced (benztropine, diphenhydramine)
- Pupil dilation for ophthalmology (tropicamide)
- Irritable bowel syndrome (dicylcomine)

2.6.2 Adverse Effects

Antimuscarinics in overdose can produce hyperthermia, tachycardia, sedation, behavioral excitation, and hallucinations. Acetylcholinesterase inhibitors are used in the management of antimuscarinic overdose.


Dose of atropine
>10.0 mg
Hallucinations and delirium; coma
5.0 mg
Rapid heart rate; palpitation; marked dryness of mouth; dilation of pupil; some blurring of near vision
2.0 mg
0.5 mg
Slight cardiac slowing; some dryness of the mouth; inhibition of sweating

▲**Figure 2-2.6** Dose-Dependent Effects of Atropine

2.7 Acetylcholinesterase Inhibitors

Acetylcholinesterase (AChE) enzymatically degrades ACh at both nicotinic and muscarinic synapses. AChE inhibitors increase the amount of ACh in the synaptic cleft.

2.7.1 Clinical Uses

AChE inhibitors have a variety of clinical uses:

- Neuromuscular reversal agents (discussed in chapter 4)
- Myasthenia gravis
- Glaucoma
- Alzheimer disease

Myasthenia Gravis This disease is caused by antibodies targeted against the muscle-type nicotinic acetylcholine receptor. Patients present with fatigue and muscle weakness. The short-acting AChE inhibitor edrophonium (Tensilon) is used to confirm a diagnosis of myasthenia gravis. For a patient with myasthenia gravis, the administration of edrophonium (the "Tensilon test") should cause rapid relief of symptoms by increasing the amount of acetylcholine able to activate nicotinic receptors. For the treatment of myasthenia gravis, the longer-acting AChE inhibitor pyridostigmine is typically used.

Glaucoma Ecothiopate is an AChE inhibitor used to treat chronic glaucoma. Similar to the use of muscarinic agonists, AChE inhibitors cause pupillary constriction and aid the drainage of aqueous humor.

Alzheimer Disease AChE inhibitors that penetrate the central nervous system are used in treating Alzheimer disease. The rationale is that there is a relative deficiency of cholinergic signaling in Alzheimer disease. The four AChE inhibitors used in Alzheimer disease are tacrine, rivastigmine, galantamine, and donepezil. These drugs tend to have limited effect, often with an improvement in symptoms for less than a year.

2.7.2 Toxicologic Importance of Acetylcholinesterase Inhibitors

AChE inhibitors are used as insecticides (parathion, malathion, chlorpyrifos) and nerve gases (VX, sarin, tabun). Given the worldwide bans on chemical weapons, nerve gas poisoning is rare. However, organophosphate AChE inhibitors are widely used as insecticides, and agriculture workers, as well as other individuals, such as children, may become exposed to these compounds.

2.7.3 Acetylcholinesterase Inhibitor Poisoning

Poisoning by an AChE inhibitor will cause an increase of acetylcholine in all cholinergic synapses and thus cause the activation of both muscarinic and nicotinic receptors. The physiologic effects include overload of the parasympathetic nervous system (increased secretions, bronchoconstriction, salivation, bradycardia, diarrhea, vomiting, and miosis) and skeletal muscle paralysis (including respiratory muscles). The treatment of AChE poisoning is supportive care (especially respiratory support), pralidoxime (2-PAM, if poisoning is by an organophosphate AChE inhibitor), and atropine. Acetylcholinesterase inhibitors are discussed in more detail in chapter 12.

Memory Aid

The mnemonic for AChE inhibitor poisoning is DUMBELSS:

Diarrhea
Urination
Miosis
Bronchoconstriction
Excitation (muscle and CNS)
Lacrimation
Salivation
Sweating

3 Adrenergic Receptors

The five adrenergic receptors are: α_1, α_2, β_1, β_2, and β_3. Clinically important drugs are available that can target each of these adrenergic receptor subtypes except the β_3-receptor.

3.1 Effects of α- and β-Adrenergic Receptors

Adrenergic receptors generally stimulate the action of the sympathetic nervous system.

- **α_1-receptors:** These receptors increase inositol triphosphate (IP3), diacylglycerol, and intracellular Ca2+. They contract smooth muscle leading to vasoconstriction and the contraction of bladder trigone and sphincter (urinary retention). Activation of α_1-receptors dilates the pupil (mydriasis).
- **α_2-receptors:** These receptors inhibit adenylyl cyclase. They constrict vascular smooth muscle but also serve as presynaptic receptors in the central nervous system that inhibit norepinephrine release.
- **β-receptors:** These receptors activate adenylyl cyclase and increase intracellular cAMP.
  - β_1-receptors are predominantly in the heart. Their action leads to increased heart rate, AV nodal conduction, and contractility.
  - β_2-receptors dilate or relax smooth muscle, causing vasodilation, bronchodilation, and uterine relaxation.

3.2 Adrenergic Receptor Sensitivity

Some drugs activate both α- and β-adrenergic receptors. With such drugs, β-receptors usually are more sensitive than α-receptors. A classic example is dopamine. An exception is norepinephrine, for which α responses predominate at lower doses. Repeated exposure to α or β agonists causes downregulation of receptors.

▼Table 2-3.2 Adrenergic Action on Target Organs and Tissue

Organ	Sympathetic		Parasympathetic	
	Action	Receptor	Action	Receptor
Heart				
SA node, heart rate	↑	β_1	↓	M
AV nodal conduction	↑	β_1	↓	M
Contractility	↑	β_1	↓ (atria only)	M
Vascular Smooth Muscle				
Skin; splanchnic	Constricts	α_1		
Skeletal muscle	Dilates	β_2		
Skeletal muscle	Constricts	α_1		
Endothelium			Releases EDRF	M
Bronchioles	Dilates	β_2	Constricts	M
Gastrointestinal Tract				
Smooth muscle, walls	Relaxes	α_2, β_2	Contracts	M
Smooth muscle, sphincters	Contracts	α_1	Relaxes	M
Saliva secretion	↓	β_1	↑	M
Gastric acid secretion			↑	M
Pancreatic secretion			↑	M
Bladder				
Wall, detrusor muscle	Relaxes	β_2	Contracts	M
Sphincter	Contracts	α_1	Relaxes	M
Male Genitalia	Ejaculation	α	Erection	M
Eye				
Radial muscle, iris	Dilates pupil (mydriasis)	α_1		
Circular sphincter muscle, iris			Constricts pupil (miosis)	M
Ciliary muscle	Dilates (far vision)	β	Contracts (near vision)	M

3.3 Adrenergic Agonists

Adrenergic agonists have a number of clinical applications.

3.3.1 α_1 Agonists

α_1-Adrenergic receptor agonists cause mydriasis, vasoconstriction, urinary retention, and contraction of smooth muscle of the prostate gland. A specific α_1 agonist is phenylephrine, a drug used to treat nasal congestion by limiting blood flow to nasal mucosa and, when given intravenously in a hospital setting, to raise blood pressure. A related drug is methoxamine. When α_1 agonists are given intravenously, they should be given in large central veins to prevent digital necrosis secondary to peripheral vasoconstriction.

3.3.2 α_2 Agonists

Clonidine and guanabenz are specific α_2-adrenergic receptor agonists. Both drugs are used to treat hypertension, and act by activating the presynaptic α_2-receptor, which has an inhibitory effect on the sympathetic nervous system. One adverse effect seen with these drugs is rebound hypertension if the drug is stopped abruptly.

3.3.3 β_1 Agonists

The prototype β_1-adrenergic receptor agonist is dobutamine, a drug used to treat cardiogenic shock and heart failure. β_1 agonists should be avoided in patients with known cardiac ischemic disease and frequent premature ventricular contractions (PVCs).

3.3.4 β_2 Agonists

β_2-Adrenergic receptor agonists are used to treat asthma and to stop premature labor.

Asthma β_2 agonists cause bronchodilation and can relieve the acute symptoms of asthma.

- **Albuterol:** A short-acting β_2 agonist used primarily for acute asthma attacks or to prevent symptoms prior to known asthma trigger (e.g., exercise, pets, cold air). Albuterol also activates β_1-receptors and can cause tachycardia and nervousness, especially with repeated use. Albuterol may be administered by inhalation or, for more severe attacks, systemically.
- **Salmeterol:** A long-acting, very selective β_2 agonist used for chronic asthma therapy.

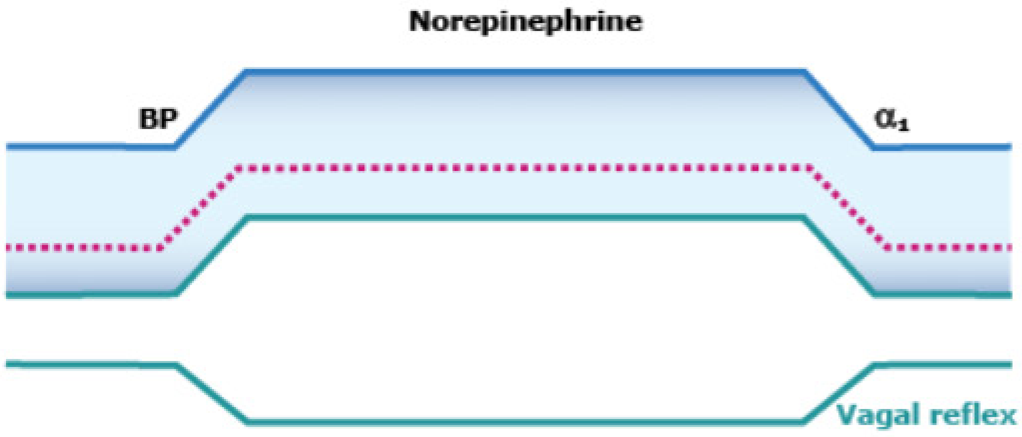
These β_2 agonists and others used to treat asthma are covered more extensively in chapter 7.

Pregnancy β_2 agonists cause relaxation of uterine smooth muscle and can slow labor. Terbutaline is a β_2 agonist that can be used to halt premature labor, usually as a temporary maneuver to allow glucocorticoids to speed fetal lung maturity. However, there are safety concerns with terbutaline, and the American College of Obstetricians and Gynecologists discourages its use to prevent preterm labor.

3.3.5 Norepinephrine

Norepinephrine is the endogenous agonist at most adrenergic synapses. When used clinically, norepinephrine has potent actions at α_1-, α_2-, and β_1-receptors but relatively little action at β_2-receptors. Norepinephrine is used in septic shock to increase blood pressure through increased peripheral vascular resistance and heart rate. After administration of norepinephrine, systolic and diastolic pressures increase (pressor effect), which triggers compensatory vagal action to slow the heart. Peripheral vascular resistance increases while cardiac output is unchanged or decreased.

One risk of norepinephrine therapy is peripheral vasoconstriction, which can lead to ischemia in the digits.



▲**Figure 2-3.3A** Norepinephrine

3.3.6 Epinephrine

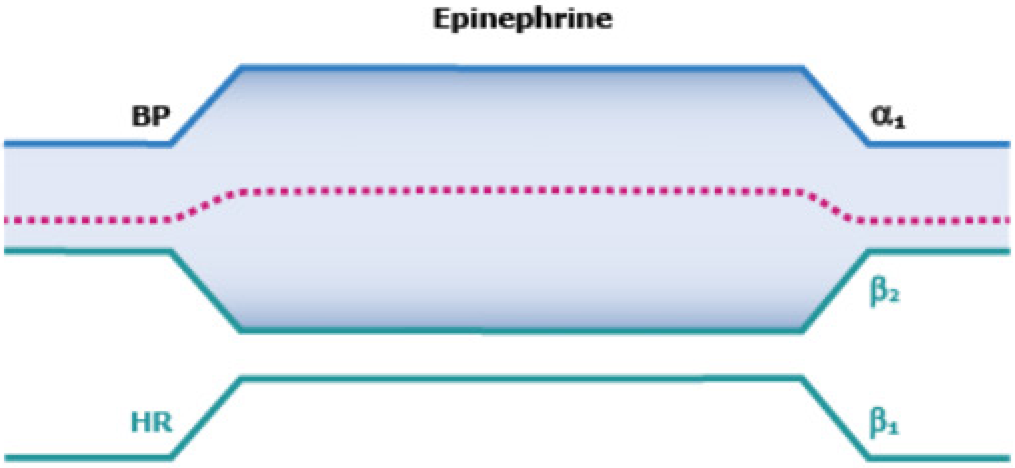
Epinephrine is a potent stimulant of both α- and β-receptors leading to complex effects on target organs. Epinephrine is used to dilate bronchial smooth muscle and raise blood pressure in patients who are very ill. Epinephrine also is used in the management of anaphylactic shock.

Administration of epinephrine causes the following effects:

- Vasocontriction of many vascular beds (especially precapillary resistance, α_1 effect).
- Increase of heart rate and contraction (β_1 effects).
- Vasodilation of large vessels in skeletal muscle (β_2 effect).
- Dilation of bronchial smooth muscle (β_2 effect).

The end result of moderate doses of epinephrine is usually a modest rise in arterial pressure (pressor effect) but with an increase in systolic pressure and a decrease in diastolic pressure. The pulse rate increases. At higher doses, the pressor effects of epinephrine become more prominent.

When epinephrine is combined with an α-adrenergic antagonist, the β agonist effects become unopposed with strong increase in heart rate (β_1) and prominent vasodilation (β_2 effect) and a drop in mean arterial pressure (reversal of pressor effect). This situation is called *epinephrine reversal.*



▲**Figure 2-3.3B** Epinephrine

3.3.7 Dopamine

Dopamine is a neurotransmitter that primarily acts at dopamine receptors. The central nervous system effects of dopamine are discussed in detail in chapter 4. However, dopamine also has important effects in the periphery and autonomic nervous system. The effects of dopamine are dose-dependent and often divided into "low-dose," "medium-dose," and "high-dose" effects.

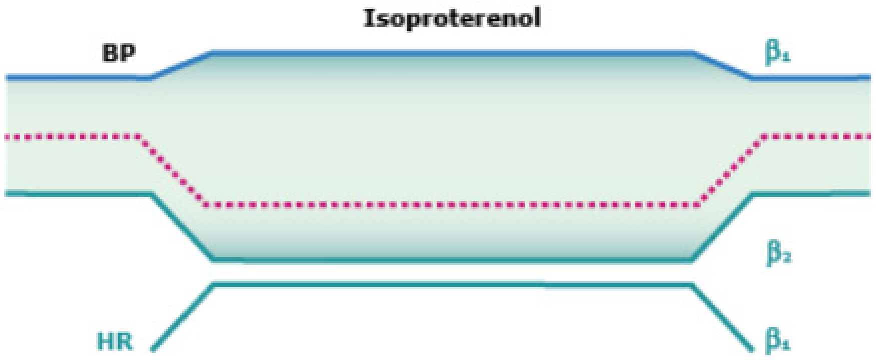
"Low-Dose" Dopamine Effects Dopamine administered at low-dose (less than 5 µg/mg/min) predominantly activates D_1 receptors leading to increased blood flow to the kidney and mesentery. Although widely used for decades to preserve renal blood flow in critically ill oligouric patients, large-scale multicenter studies have failed to demonstrate clinical benefit to this practice.

"Medium-Dose" Dopamine Effects Dopamine administered at medium-does (5-15 µg/mg/min) activates β_1-adrenergic receptors in addition to D_1 receptors. This increases cardiac output and can be useful in shock states; however, there is risk of cardiac arrhythmias.

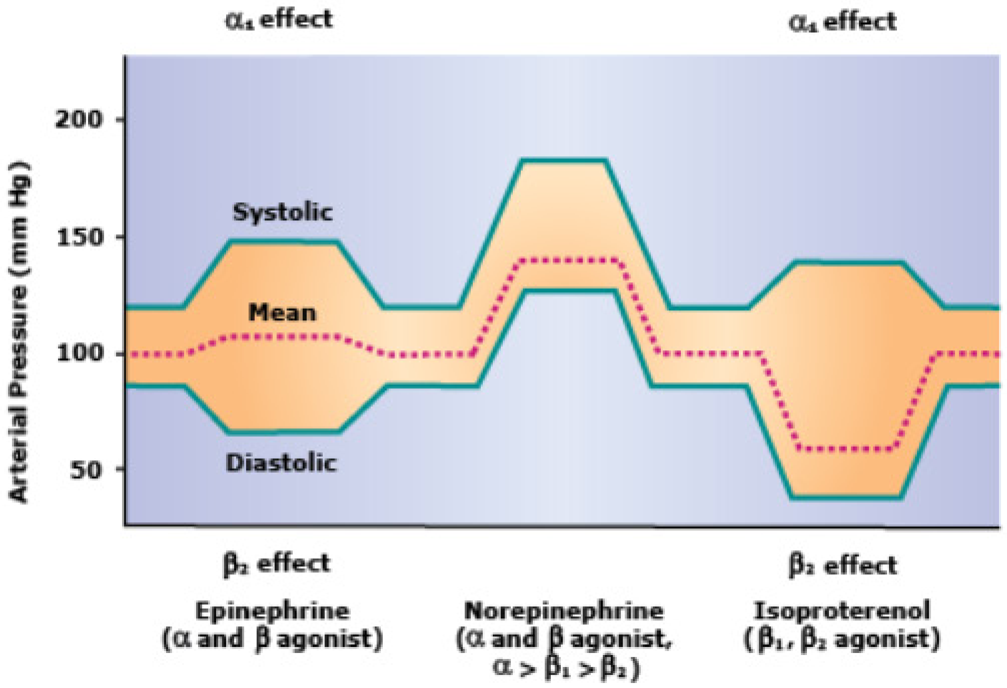
"High-Dose" Dopamine Effects Dopamine administered at high-dose (greater than 15 µg/mg/min) activates α_1-adrenergic receptors in addition to the low- and medium-dose effects described above. This raises systolic blood pressure but carries a risk of peripheral ischemia (and possible necrosis and gangrene) because of vasoconstriction, especially in patients with shock.

3.3.8 Isoproterenol

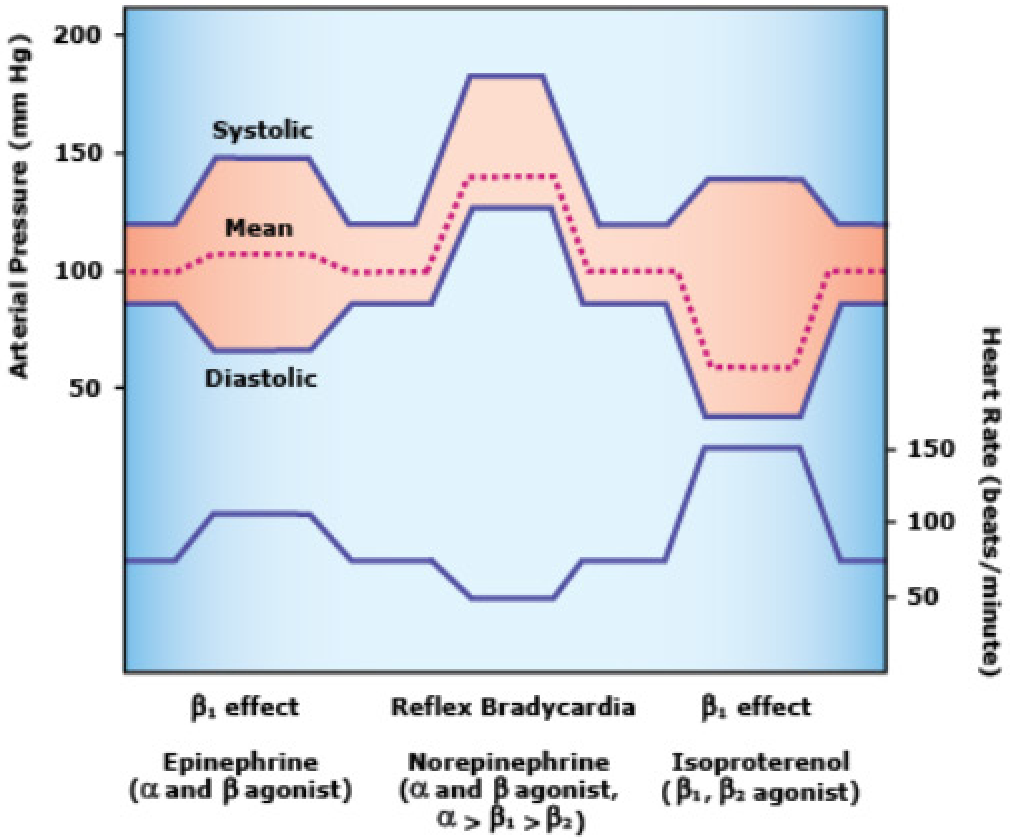
Isoproterenol is a nonselective β-adrenergic agonist that lowers peripheral vascular resistance (β_2 effect) and increases heart rate and contractility (β_1 effect). Isoproterenol is used primarily in symptomatic bradycardia, sometimes as a bridge to pacemaker placement. The effects of isoproterenol are blocked by a nonselective β-blocker such as propranolol or nadolol.



▲**Figure 2-3.3C** Isoproterenol



▲**Figure 2-3.3D** Effects of Norepinephrine, Epinephrine, and Isoproterenol on Blood Pressure



▲**Figure 2-3.3E** Effects of Norepinephrine, Epinephrine, and Isoproterenol on Heart Rate

3.3.9 Tyramine

Tyramine is a naturally occurring amine found in the highest amounts in aged cheese, fava beans, beer, and Chianti wine. Tyramine is normally rapidly metabolized by monoamine oxidase A (MAO-A) in the gastrointestinal tract and liver.

Tyramine displaces norepinephrine from synaptic vesicles. Normally, this is of little physiological consequence. However, patients taking MAO-A inhibitors (e.g., phenelzine, tranylcypromine) may experience "tyramine crisis" if ingesting food or drinks with high levels of tyramine. Very high concentrations of tyramine can cause a massive leak of norepinephrine from synaptic vesicles, leading to hypertensive crisis. Patients taking MAO-A inhibitors should avoid tyramine in their diets.

3.4 Adrenergic Antagonists

Adrenergic receptor antagonists include some of the most commonly used medication, such as the β-blockers.

3.4.1 α Antagonists

α Antagonists can be divided into specific (block α_1- or α_2-receptors only) and nonspecific (block α_1 and α_2).

α_1-Specific Antagonists These include prazosin, doxazosin, terazosin, and tamsulosin. Prazosin and doxazosin are used to treat hypertension. Terazosin and tamsulosin are used for benign prostatic hyperplasia and work by relaxing prostatic capsular smooth muscle. All α_1 antagonists are capable of causing orthostatic hypotension. Prazosin is especially noted for "first dose effect," a potential large drop in blood pressure in early dosing.

α_2-Specific Antagonists Yohimbine is a specific α_2-receptor antagonist. It is not used clinically but is purported to have aphrodisiac effects.

Nonspecific Antagonists Phenoxybenzamine and phentolamine block both α_1- and α_1-receptors. Phenoxybenzamine acts irreversibly. These drugs are used in the medical management of pheochromocytoma to block the effects of catecholamines released by tumors, often as a temporary measure until surgery can be performed.

3.4.2 β Antagonists

Antagonists of β-adrenergic receptors, or "β-blockers," are commonly used medications. These drugs may inhibit β_1-receptors only, both β_1- and β_2-receptors, and even α_1-receptors in addition to β_1- and β_2-receptors.

Selectivity of β-blockers

- Selective antagonists of β_1-receptors include atenolol, metoprolol, and esmolol.
- Nonselective β-blockers antagonize both β_1-and β_2-receptors. Examples include propranolol (prototype) and nadolol.
- Two drugs, carvedilol and labetalol, block α_1- as well as β_1- and β_2-receptors.

▼Table 2-3.4A Selectivity of β-Adrenoceptor Antagonists

Drug	Notes
Nonselective β-Adrenergic Antagonists	
Propanolol	Short half-life
Nadolol	Long half-life
Timolol	Lipophilic-high CNS penetration
Nonselective β- and α_1-Adrenergic Antagonists	
Labetalol	Also partial agonist at β_2-receptors
Carvedilol	Intermediate half-life
β-Adrenergic Partial Agonists	
Pindolol	β-nonselective
Acebutolol	β_1-selective
β_1-Selective Adrenergic Antagonists	
Esmolol	Short half-life (4 minutes)
Metoprolol	Intermediate half-life
Atenolol	Intermediate half-life

Duration of Action of β-blockers Clinically used β-blockers demonstrate a range of duration of action. Esmolol is an intravenously administered β-blocker with a very short duration of action (minutes). It is used for acute management of certain cardiac arrhythmias. Nadolol and carvedilol are longer acting (half-life of one day or greater).

β-blockers With Partial Agonist Effect Two β-blockers, acebutolol and pindolol, are actually weak partial agonists at β-receptors, a phenomenon also known as *intrinsic sympathomimetic activity.* These agents act as antagonists when there is high adrenergic activity because they displace norepinephrine and have lower efficacy. The theoretic advantage of these partial agonists is that they should cause less bradycardia and other adverse effects because they have some agonist activity. However, partial agonist β-blockers have not been widely prescribed in the United States.

Clinical Uses of β-blockers Clinical uses are broad and include:

- Hypertension
- Cardiac arrhythmias
- Heart failure
- Angina
- Anxiety
- Muscle tremors
- Hyperthyroidism
- Glaucoma

The use of β-blockers in treating hypertension, cardiac arrhythmias, heart failure, and angina is discussed in chapter 3.

Nonselective β-blockers, such as propranolol, are used in treating anxiety, muscle tremors, and hyperthyroidism because β_2-receptors are involved in these disorders.

In the treatment of open-angle glaucoma, a nonselective β-blocker, timolol, is used topically to reduce aqueous humor secretion.

Labetalol is used in cocaine overdose to block the excess sympathetic effects.

Adverse Effects of β-blockers These include:

- Bradycardia
- AV conduction block
- Hypotension
- Sexual dysfunction

Nonselective β-blockers should be avoided in asthma patients due to bronchoconstriction cause by blocking β_2-receptors. Nonselective agents also can cause problems in diabetic patients by blocking glycogenolysis (a β_2 effect). This may present issues in diabetic patients who depend on adrenergic-mediated glycogenolysis to raise blood glucose levels. In addition, all β-blockers can mask the sympathetic symptoms (e.g., tachycardia) that warn diabetic patients of hypoglycemia.

▼**Table 2-3.4B** Classic Adrenergic Agonists and Antagonists

Rows	Agonists	Antagonists
Adrenoreceptors		
α_1	Norepinephrine Phenylephrine	Phenoxybenzamine Prazosin, Terazosin
α_2	Clonidine	Yohimbine
β_1	Dobutamine Isoproterenol	Propranolol Metoprolol
β_2	Albuterol Isoproterenol Salmeterol	Propranolol
Cholinoreceptors		
Nicotinic	ACh Nicotine	Curare Hexamethonium (blocks ganglionic receptor but not neuromuscular junction)
Muscarinic	ACh Muscarine Carbachol	Atropine

4 Histaminergic Receptors

Histamine is an autacoid (locally acting compound) present at high levels in lungs, skin, and the gastrointestinal tract. Histamine is released from mast cells in response to type I (IgE-mediated) hypersensitivity reactions, drugs (e.g., mivacurium, vancomycin), venoms, and trauma. Histamine receptors are G-protein coupled receptors with two classes, termed H_1 and H_2.

4.1 Histamine-1 Receptors

Histamine-1 (H_1) receptors are found in a variety of tissues, including skin, blood vessels, and the brain. Activation of H_1 receptors in the periphery produces capillary dilation, decreased blood pressure (vasodilation), bronchiolar smooth muscle contraction, pain, and pruritus. Activation of CNS H_1 receptors produces arousal. H_1 receptor antagonists are widely used. There is no clinical role for H_1 receptor agonists.

H_1 receptor antagonists are used for a variety of clinical applications:

- Treatment of allergic reactions (hay fever, rhinitis, urticaria)
- Prevention and treatment of motion sickness
- Sedation
- Over-the-counter sleep aids

First-generation H_1 receptor antagonists penetrate the CNS and are sedating. The prototype is diphenhydramine (Benadryl). Diphenhydramine also has antimuscarinic effect. Another first-generation H_1 receptor antagonist is hydroxyzine.

Second-generation H_1 receptor antagonists do not penetrate the CNS and in general are not sedating ("non-drowsy"). Common examples are cetirizine (Zyrtec), loratadine (Claritin), and fexofenadine (Allegra).

4.2 Histamine-2 Receptors

Histamine-2 (H_2) receptors are important in gastric acid secretion and indirectly stimulate parietal cell proton pump activity. The main clinical importance of H_2 receptors is in the use of antagonists, which are used in the management of stomach ulcers and gastroesophageal reflux disease. The most commonly used H_2 receptor antagonists are cimetidine (Tagamet), famotidine (Pepcid), and ranitidine (Zantac). These antagonists are discussed in detail in chapter 8.

5 Serotonergic Receptors

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter synthesized and stored in gastrointestinal cells, neurons, and platelets. Serotonin is metabolized by monoamine oxidase type A (MAO-A) and also cleared from synapses by the serotonin transporter.

5.1 Serotonin and Carcinoid Tumors

5-HT is released by carcinoid tumors and may produce symptoms such as flushing, diarrhea, wheezing, and peripheral edema. Diagnosis of carcinoid tumors is aided by assays for the major metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA). The somatostatin analog octreotide is used to treat carcinoid tumors. The activation of somatostatin receptors has an inhibitor effect on carcinoid tumors and leads to less release of serotonin.

5.2 Serotonin Receptors

There are numerous serotonin receptors that currently fall into seven receptor-subtypes. All are coupled to G-coupled second messenger systems except the 5-HT_3 receptor, which is a ligand-gated ion channel. The 5-HT_3 receptor antagonists are used to treat nausea and vomiting and are discussed in chapter 8.

5.3 Drugs Affecting the Serotonin System

Many clinically used drugs affect the serotonergic system, either by activating or antagonizing serotonin receptors, or by the action of serotonin receptors or MAO-A.

5.3.1 Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs inhibit the serotonin transport and raise serotonin levels throughout the brain. These drugs are widely used to treat depression, phobias, and obsessive-compulsive disorder, and are discussed in detail in chapter 4.

5.3.2 Buspirone

Buspirone (Buspar—not to be confused with similar sounding buproprion) is a 5-HT_{1A} receptor partial agonist used to treat anxiety.

5.3.3 Atypical Antipsychotics

Many of the atypical antipsychotics used to treat schizophrenia (e.g., clozapine, risperidone) block the 5-HT_2 receptor. These drugs are discussed in detail in chapter 4.

5.3.4 Hallucinogens

Lysergic acid diethylamide (LSD, "acid") and some plant- or fungus-derived hallucinogens (e.g, mescaline from cactus or psilocybin from mushrooms) act as 5-HT_2 receptor agonists. Note that this pharmacologic effect is the opposite of certain antipsychotic agents.

5.3.5 Triptans and Other Migraine Therapies

Triptans (e.g., sumatriptan, rizatriptan) are drugs used to treat and prevent migraine headaches. These drugs act as 5-HT$_{1D}$ receptor agonists and appear to act in part by reducing cerebral vasodilation that occurs in migraines. Triptans have few side effects but can cause shifts in blood pressure and, in heavier doses, sulfhemoglobinemia, which may present as cyanosis.

Ergot alkaloids are older drugs used for migraines (often in combination pills that also contain caffeine) that activate multiple serotonin receptors including the 5-HT$_{1D}$ receptor. Ergotamine is used to treat migraines, although its use is declining given the increasing popularity of the triptans. Ergotamine may cause gastrointestinal irritation and drowsiness. Ergotamine is category X in pregnancy due to the risk of uterine contractions and the subsequent risk of abortion or premature delivery.

6 Eicosanoids (Lipid-Derived Autacoids) and the Nonsteroidal and Anti-inflammatory Drugs

Eicosanoids are locally acting mediators (autacoids) derived from membrane phospholipids that have diverse roles in inflammation and cell signaling. Clinically important eicosanoids include prostaglandins, prostacyclin, leukotrienes, and thromboxane A_2.

6.1 Synthesis and Function of Eicosanoids

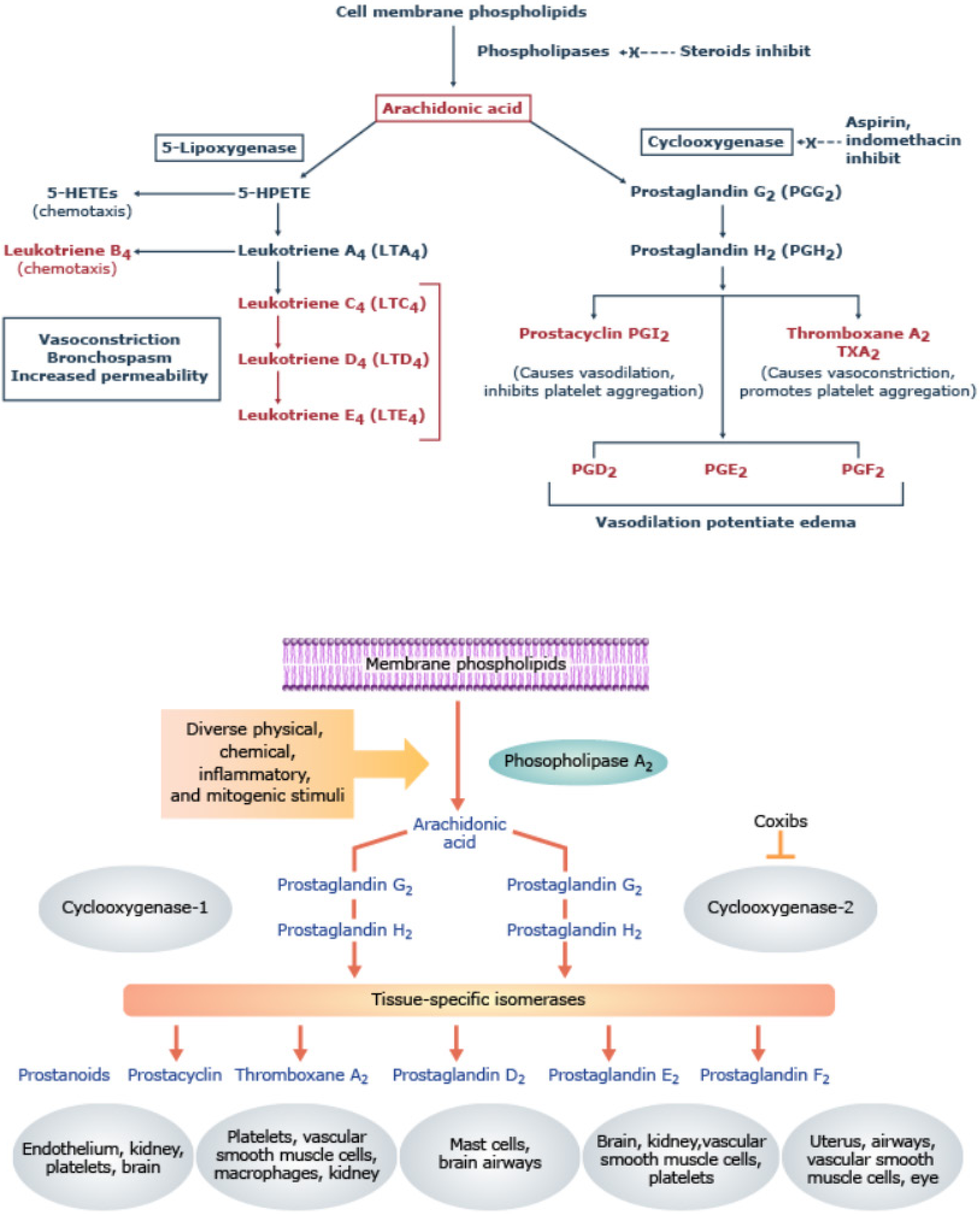
Eicosanoids are derived from arachidonic acid, which in turn is synthesized from linoleic acid (an essential dietary fatty acid). Arachidonic acid is released from membrane phospholipids by the enzyme phospholipase A_2 (PLA_2). Eicosanoids usually are present in low concentrations but are synthesized in higher amounts in response to inflammation, trauma, toxins, and infection. Prostaglandin H_2 (PGH_2) is formed by cyclooxygenases (COXs, previously known as prostaglandin synthases). PGH_2 in turn is converted to a variety of specific compounds by tissue-specific enzymes.

6.1.1 Cyclooxygenase-1 (COX-1)

COX-1 is expressed in most tissues and shows constitutive expression (generally not inducible). Two important functions of the prostaglandins produced by COX-1 are to help protect gastric mucosa and maintain vascular homeostasis.

6.1.2 Cyclooxygenase-2 (COX-2)

COX-2 is expressed in the brain, kidney, and at sites of inflammation. In contrast to COX-1, COX-2 is inducible and activity may increase 20- to 80-fold in response to infection and inflammation, mediated by factors such as tumor necrosis factor-α, other cytokines, and bacterial lipopolysaccharide.


Cell membrane phospholipids
Phospholipases
Steroids inhibit
Arachidonic acid
5-Lipoxygenase
Cyclooxygenase
Aspirin, indomethacin inhibit
5-HETEs (chemotaxis)
5-HPETE
Leukotriene B_4 (chemotaxis)
Leukotriene A_4 (LTA_4)
Leukotriene C_4 (LTC_4)
Leukotriene D_4 (LTD_4)
Leukotriene E_4 (LTE_4)
Vasoconstriction
Bronchospasm
Increased permeability
Prostaglandin G_2 (PGG_2)
Prostaglandin H_2 (PGH_2)
Prostacyclin PGI_2
(Causes vasodilation, inhibits platelet aggregation)
Thromboxane A_2 TXA_2
(Causes vasoconstriction, promotes platelet aggregation)
PGD_2
PGE_2
PGF_2
Vasodilation potentiate edema
Membrane phospholipids
Diverse physical, chemical, inflammatory, and mitogenic stimuli
Phospholipase A_2
Arachidonic acid
Coxibs
Cyclooxygenase-1
Prostaglandin G_2
Prostaglandin H_2
Prostaglandin G_2
Prostaglandin H_2
Cyclooxygenase-2
Tissue-specific isomerases
Prostanoids
Prostacyclin
Thromboxane A_2
Prostaglandin D_2
Prostaglandin E_2
Prostaglandin F_2
Endothelium, kidney, platelets, brain
Platelets, vascular smooth muscle cells, macrophages, kidney
Mast cells, brain airways
Brain, kidney,vascular smooth muscle cells, platelets
Uterus, airways, vascular smooth muscle cells, eye

▲**Figure 2-6.1** Arachidonic Acid Metabolism

6.1.3 Prostaglandin D_2 (PGD_2)

PGD_2 is produced by mast cells and causes smooth muscle contraction, including bronchoconstriction.

6.1.4 Prostaglandin E_2 (PGE_2)

PGE_2 is expressed in many tissues and mediates a number of functions:

- Protection of gastric mucosa
- Inflammatory effects
- Vasodilation
- Fever (hypothalamus-mediated)
- Uterine contraction

There is overlap in the pharmacologic activity of drugs with PGE_1 and PGE_2 activities.

Misoprostol (Cytotec) This PGE_1 analog is used to protect the gastric mucosa in the treatment of NSAID-induced ulcers (discussed in more detail in chapter 8). Misoprostol is also used in combination with the antiprogestin drug mifepristone (RU-486) to induce abortion in the first trimester. Mifepristone interferes with the actions of progesterone on the developing fetus, and misoprostol causes uterine contractions.

Alprostadil This PGE_1 analog is used in newborns with certain congenital heart defects (transposition of the great vessels, coarctation of the aorta, valvular atresia) to maintain a patent ductus arteriosus prior to cardiac surgery.

Alprostadil also is used as an injectable for intracavernous administration to treat erectile dysfunction. This use of alprostadil has declined with the introduction of sildenafil (Viagra), tadalafil (Cialis), and related oral agents for erectile dysfunction.

Dinoprostone Dinoprostone is a PGE_2 analog used to progress labor by inducing uterine smooth muscle contraction.

6.1.5 Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)

$PGF_{2\alpha}$ is produced by vascular and uterine smooth muscle. Increased levels can induce abortion.

Carboprost This $PGF_{2\alpha}$ analog is used to induce abortion and to stop postpartum hemorrhage by causing strong uterine contractions.

$PGF_{2\alpha}$ Analogs Used for Glaucoma Latanoprost, bimatoprost, and travoprost are $PGF_{2\alpha}$ analogs used topically in the eye to treat ocular hypertension and open-angle glaucoma. These drugs cause vasodilation in the eye.

Important Concept

There is overlap in the pharmacologic activities of PGE_1, PGE_2, and $PGF_{2\alpha}$. For example, all three prostaglandins can induce uterine contractions.

6.1.6 Thromboxane A_2 (TXA_2)

TXA_2 is the chief eicosanoid product of platelets and is exclusively produced by the COX-1 pathway. TXA_2 is a strong vasoconstrictor and promoter of platelet adhesion and aggregation.

6.1.7 Prostacyclin I_2 (PGI_2)

PGI_2 is the chief eicosanoid product of the vascular endothelium and is exclusively produced by the COX-2 pathway. PGI_2 is a vasodilator and inhibitor of platelet aggregation.

6.2 Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are some of the most commonly used drugs. The traditional NSAIDs (aspirin, ibuprofen, naproxen) are nonselective inhibitors of both COX-1 and COX-2. The selective COX-2 inhibitors (celecoxib, rofecoxib) are newer drugs that cause more COX-2 than COX-1 inhibition.

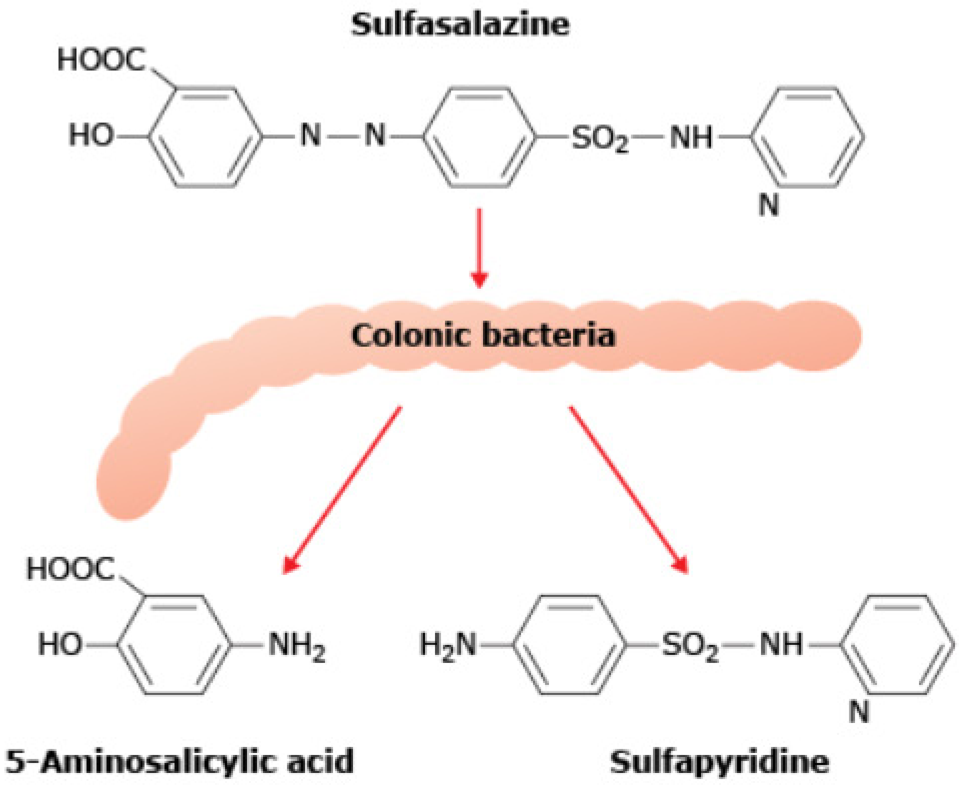
6.2.1 Aspirin

Aspirin is an irreversible inhibitor of COX-1 and COX-2. Aspirin nearly completely inhibits COX-1 and only partially inhibits COX-2. It is the only NSAID that acts irreversibly. Aspirin is used clinically for inhibition of platelet aggregation (e.g., to reduce the risk of myocardial infarction), analgesia, fever reduction (antipyresis), and anti-inflammatory effect.

Antiplatelet Actions of Aspirin The irreversible inhibition of COX-1 by aspirin prevents platelets from making TXA_2. This shifts the balance toward PGI_2 vasodilation and anti-thrombogenesis. Because platelets lack nuclei, new platelets need to be synthesized to overcome aspirin effect. Low-dose (81 mg) aspirin is well-documented to reduce the risk of myocardial infarction and stroke.

Salicylate Derivatives Used in Inflammatory Bowel Disease Salicylate derivatives are used for intragut treatment of inflammatory bowel disease. For ulcerative colitis or Crohn disease confined to the colon, sulfasalazine may be used. Sulfasalazine is a drug that is dissociated in the colon by colonic bacteria to 5-aminosalicylic acid, which acts locally in the colon and is not absorbed systemically.

Enema preparations of salicylates also may be used in inflammatory bowel disease affecting the colon.



▲ **Figure 2-6.2** Sulfasalazine

Important Concept

The balance between TXA_2 and PGI_2 is critical for the regulation of blood pressure and thrombogenesis. This balance may be disrupted by drugs such as the selective COX-2 inhibitors.

Aspirin Adverse Effects Aspirin can produce a variety of adverse effects, especially with chronic usage:

- Gastrointestinal irritation (ulcers, GI bleeding)
- Bleeding complications
- Nephrotoxicity

The irreversible action of aspirin on platelets can cause increased bleeding risk when aspirin has been used within one week of surgery or some other invasive procedure.

Reye Syndrome This syndrome is a rare, fulminant hepatoencephalopathy associated with aspirin use and influenza B and varicella-zoster infections.

Aspirin-Induced Bronchoconstriction Also known as aspirin-induced airway hyperreactivity, this form of bronchoconstriction is seen in approximately 10% of asthma patients. One possible cause is that blockade of the COX pathways shunts arachidonic acid toward increased leukotriene synthesis. A number of the leukotrienes have bronchoconstrictive effects. Drugs that inhibit the leukotriene system for the treatment of asthma are discussed in chapter 7.

Aspirin Overdose This is a potentially life-threatening medical emergency. Early signs of toxicity are tinnitus and vertigo. Later signs include hyperpyrexia and tachypnea (both likely due to aspirin effects on the brain) and bleeding. Aspirin overdose causes a complex acid-base disorder with metabolic acidosis (due to aspirin being a weak acid) and respiratory alkalosis (due to tachypnea mediated by a central effect, not just compensation for metabolic acidosis). The end result can be a "normal" pH but with markedly abnormal bicarbonate and pCO_2 on the arterial blood gas.

Aspirin overdose is managed with aggressive supportive therapy. Bicarbonate infusion can aid renal elimination (discussed in chapter 1).

6.2.2 Nonselective NSAIDs Other Than Aspirin

A variety of drugs other than aspirin are nonselective inhibitors of COX-1 and COX-2. Examples include ibuprofen, naproxen, and indomethacin. Naproxen has the longest half-life of these drugs.

Like aspirin, other nonselective NSAIDs are used for analgesic, antipyretic, and anti-inflammatory actions. The main contrast with aspirin is that other NSAIDs are not commonly used for antiplatelet effects. The reversible action of NSAIDs other than aspirin means the antiplatelet effect for these drugs is much less sustained and reliable.

Nonselective NSAIDs other than aspirin can produce similar adverse effects to aspirin. They are not, however, associated with Reye syndrome, airway hyperreactivity, or complex acid-base disorder.

6.2.3 Selective COX-2 Inhibitors

The selective COX-2 inhibitors block COX-2 more than COX-1. The prototype drugs are celecoxib (Celebrex), rofecoxib (Vioxx), and meloxicam (Mobic). The strategy behind these drugs was to avoid COX-1 inhibition and thereby avoid adverse effects such as gastric ulcers. These drugs have similar anti-inflammatory effects to traditional NSAIDs.

The COX-2 inhibitors were heavily marketed but safety concerns began to surface in 2002. Most notably, COX-2 inhibitors showed an increased risk of cardiovascular adverse events, thought to be due to upsetting the balance between TXA_2 and PGI_2. The most selective COX-2 inhibitor, rofecoxib, was withdrawn from the market in 2004.

Clinical use of COX-2 inhibitors should include discussion with patients on the risks versus benefits. In some circumstances, such as a patient with a history of gastric ulcers, COX-2 inhibitors provide a clear advantage over traditional NSAIDs.

6.3 Acetaminophen

Acetaminophen has a unique pharmacologic profile relative to the traditional NSAIDs. It does not inhibit COX-1 or COX-2 to any significant degree and lacks significant anti-inflammatory effects. Acetaminophen does have excellent analgesic and antipyretic activity, with an unknown mechanism of action.

6.3.1 Acetaminophen vs. Traditional NSAIDs

Acetaminophen has a number of distinct differences relative to traditional NSAIDs:

- Little anti-inflammatory action
- No antiplatelet action
- Not implicated in Reye syndrome
- Not bronchospastic
- Minimal effects on the gastrointestinal tract, particularly with regard to ulcers

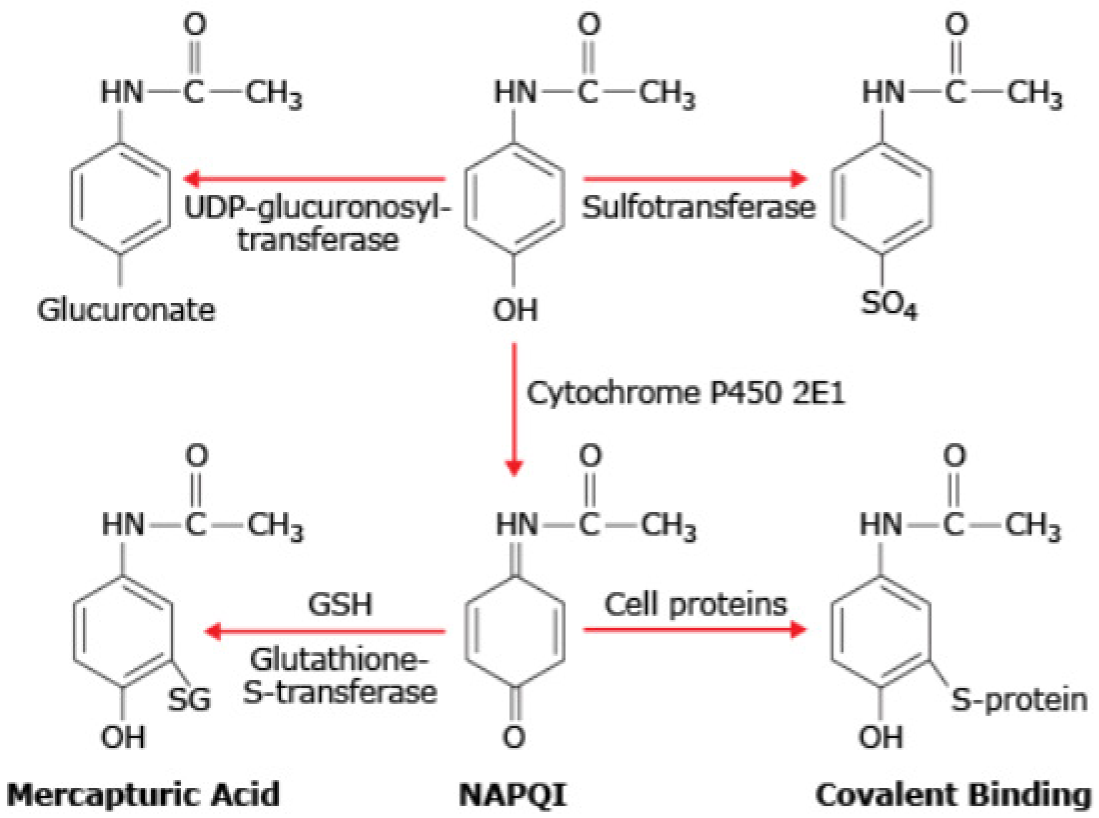
When used properly, acetaminophen has a better safety profile in children relative to aspirin.

6.3.2 Acetaminophen Overdose

Unfortunately, acetaminophen overdose can be disastrous and is currently a leading cause of acute liver failure resulting in death or liver transplantation, particularly in teenagers and young adults. Ingestion of 7 to 8 grams or more of acetaminophen in adults can cause severe liver injury. The combination of acetaminophen with opiates in certain formulations (e.g., hydrocodone + acetaminophen = Vicodin) means that an overdose of those products can lead to both opiate and acetaminophen toxicity.

Metabolism Acetaminophen is metabolized mainly by glucuronidation (phase 2 metabolism) to form an inactive conjugate. Sulfation also plays a minor role in metabolism. However, in acetaminophen overdose, there is a third pathway mediated by CYP2E1 that becomes important and can produce a toxic reactive metabolite (*N*-acetyl-*para*-benzoquinonimine, or NAPQI). Normally, NAPQI is detoxified by glutathionation, but large overdoses overwhelm the glutathionation capacity and NAPQI damages cellular proteins in the liver. The classic presentation is centrilobular necrosis and liver failure.

A patient's chronic use of ethanol enhances the potential for liver failure due to induction of CYP2E1. Interestingly, acute use of ethanol can provide some protection against acetaminophen by competing for the CYP2E1 enzyme and limiting the production of NAPQI.


HN—C—CH3
O
Glucuronate
UDP-glucuronosyl-transferase
OH
Sulfotransferase
SO4
Cytochrome P450 2E1
GSH
Glutathione-S-transferase
SG
Cell proteins
S-protein
Mercapturic Acid
NAPQI
Covalent Binding

▲**Figure 2-6.3** Acetaminophen Metabolism

Management of Acetaminophen Overdose The antidote for acetaminophen overdose is *N*-acetylcysteine (Mucamyst), a drug that replenishes glutathione stores and helps detoxify NAPQI. *N*-acetylcysteine is most effective when used within the first 12 hours following acetaminophen overdose. Beyond 12 hours, irreversible damage starts to occur and the effectiveness of the antidote is limited. The Rumack-Matthew nomogram is often used to determine whether *N*-acetylcysteine is necessary.

Chapters 1–2 Review Questions

1. You want to administer gentamicin for suspected gram-negative sepsis in a 55-year-old male. He weighs 110 kg and is 40 kg above his ideal (lean) body weight. Your pharmacology manual suggests that the dosing weight for gentamicin should be calculated with the following formula:

> Dosing weight = (lean body weight) + [1/4 × (obese weight)]

You find that the V_d of gentamicin is 0.3 L/kg (using dosing weight) and the $t_{1/2}$ is 2 hours. Based on this information, what would be the *appropriate loading dose,* assuming you desire a peak plasma concentration of 7 µg/mL?

A. 50 mg
B. 147 mg
C. 168 mg
D. 231 mg
E. 334 mg

2. A 45-year-old female morphine addict runs out of morphine during a drug binge. To continue her high, she obtains a large amount of pentazocine and consumes it. However, rather than feeling an opioid high, she experiences nausea, vomiting, restlessness, and an intense craving for morphine, as she did in the past when she suddenly stopped taking morphine. At that point, she does not take any other opiates for a week, but takes more pentazocine and gets a high similar to taking morphine, but milder. Based on this information, what type of opioid analgesic is pentazocine?

A. Full agonist
B. Competitive antagonist
C. Noncompetitive antagonist
D. Partial agonist
E. Inverse agonist

Review Questions Chapters 1–2

3. A patient was admitted to the ER 2 hours after taking an overdose of phenobarbital. The plasma level at time of admission is 100 mg/L, the apparent V_d is 35 L, the half-life is 4 days, and the clearance of phenobarbital is 6.1 L/day. The ingested dose was approximately what?

A. 1 g
B. 3.5 g
C. 6.1 g
D. 40 g
E. 70 g

4. A 59-year-old female who recently received a renal transplant is maintained on cyclosporine to prevent organ rejection. She now needs treatment for hypertension, gastroesophageal reflux, and tuberculosis, and is started on cimetidine, rifampin, pyrazinamide, hydrochlorothiazide, and metoprolol. After several weeks of therapy, she returns to the clinic for a follow-up and is found to have markedly elevated cyclosporine plasma concentrations, raising concern for nephrotoxicity. Which other drug that she was taking *most likely* caused the cyclosporine levels to become toxic?

A. Cimetidine
B. Rifampin
C. Pyrazinamide
D. Hydrochlorothiazide
E. Metoprolol

Chapters 1–2 Review Questions

5. The local anesthetic lidocaine is a weak base, with a pK_a of about 8.0. At a physiologic pH (assume = 7.0 for calculation purposes), approximately what percentage of the lidocaine will be in a form able to cross nerve membranes?

A. 0.1%
B. 1%
C. 10%
D. 90%
E. 99%

6. If lidocaine, with a pK_a of approximately 8, is injected into an infected tissue with a pH of approximately 5.0, about what percentage of the lidocaine will be in a form able to cross nerve membranes?

A. 0.1%
B. 1%
C. 10%
D. 90%
E. 99%

Review Answers Chapters 1–2

1. The correct answer is C. 168 mg. This is a complicated question that incorporates several concepts. Gentamicin is a larger molecule that distributes mainly in vascular fluid and not in adipose. Therefore, the weight used to estimate volume of distribution only incorporates a fraction of the added weight in patients who are obese.

Dosing weight = (lean body weight) + [¼ × (obese weight)]

Dosing weight = 70 kg + (¼ × 40 kg) = 80 kg

Vd = 0.3 L/kg × 80 kg = 24 L

Css = 7 µg/mL x 1 mg/1,000 µg × 1,000 mL/L = 7,000 mg/L/1,000 = 7 mg/L

Loading dose = Css x V_d/bioavailability

Loading dose = (7 mg/L) × 24 L = 168 mg

2. The correct answer is D. Partial agonist. Pentazocine (Talwin) is a partial agonist at the opioid µ receptor. When used by itself in lower therapeutic doses, pentazocine produces typical opioid effects similar to morphine. However, when used in higher doses by someone who is also taking a full opioid agonist such as morphine, pentazocine can act as an opiate antagonist and trigger a full-blown withdrawal syndrome in the morphine addict.

3. The correct answer is B. 3.5 g. This is an example of a question that requires some analysis. There are two keys to this question: (a) long half-life of the drug and (b) plasma level measured very close to time of ingestion. This means that it is in essence a "loading-dose" calculation. Clearance and half-life are not needed to solve the problem—*it is common in boards questions for extraneous information to be included.* The following formula would be used to calculate the amount of drug that would cause a plasma level of 100 mg/L with a V_d of 35 L:

C_p = dose/V_d

OR

Dose = C_p x V_d = 100 mg x 35 L = 3,500 mg
3,500 mg × 1 g/1,000 mg = 3.5 g

4. The correct answer is A. Cimetidine decreases the clearance of cyclosporine by inhibiting cytochrome P450 (CYP) metabolism. Cimetidine has interactions with multiple other drugs due to its ability to inhibit CYP metabolism. Of the other choices listed, rifampin is an inducer (not inhibitor) of CYP enzymes. The other drugs listed have minimal effects on CYP metabolism.

5. The correct answer is C. 10%. Local anesthetics are weak bases. In this case:

HB^+/B = pK_a − pH = 1 (the antilog of 1 is 10).

HB^+/B = 10/1= 100/10; this represents 10% non-ionized at pH = 7.0, which is the form that can cross the neural membranes and block voltage-gated sodium channels and cause local anesthesia.

6. The correct answer is A. 0.1%. In this case, from the Henderson-Hasselbalch relationship, this represents 0.1% non-ionized.

HB^+/B = pK_a − pH

HB^+/B = 8 − 5 = 3 (the antilog of 3 is 1,000)

HB^+/B = 1,000/1 = 100/0.1

So, at a lower pH of 5, less than 1% of lidocaine is in the uncharged form, so less than 1% will be absorbed at this lower pH. This is why local anesthetics have reduced activity when injected into infected tissues such as abscesses. At acidic pH, most of the drug is ionized and unable to cross nerve cell membranes.

CHAPTER 3 Cardio Pharmacology

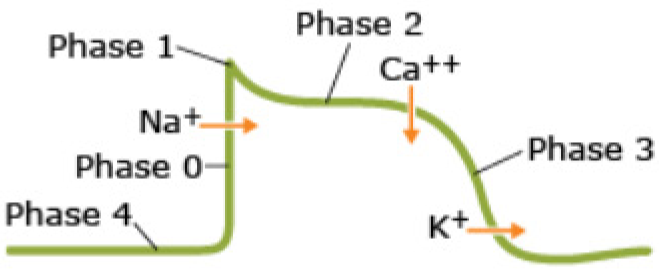
1 Antiarrhythmics

The antiarrhythmics are a diverse class of drugs that can alter cardiac rhythms. The use of these drugs has been steadily fading due to increased use of interventional cardiology procedures and pacemaker placements. Amiodarone and sotalol are the most widely used antiarrhythmics in the United States.

1.1 Classifications

The most commonly used classification system for antiarrhythmic drugs is the Vaughn Williams classification, which groups drugs based on their primary mechanism of action. This system is organized around the receptor or ion channel with which the drugs interact and has five major classes:

- Class I: Sodium channel blockers
- Class II: β-adrenergic receptor blockers
- Class III: Potassium channel blockers
- Class IV: Calcium channel blockers
- Class V: Miscellaneous



▲**Figure 3-1.1** Cardiac Myocte/Pacemaker Action Potential

1.2 Class I: Na^{+} Channel Blockers

Class I antiarrhythmics block fast sodium channels responsible for early, rapid depolarization phase of AP (Phase 0).

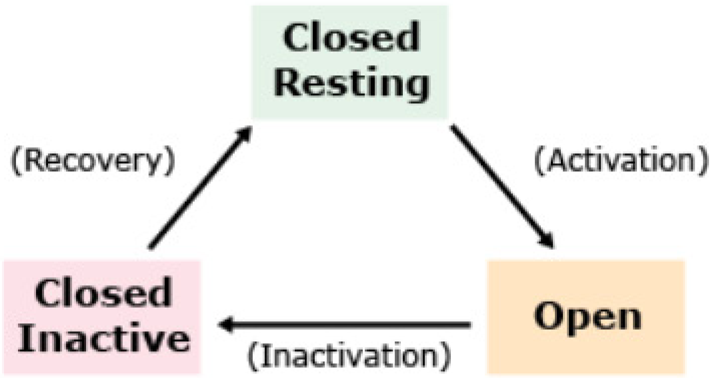
This group of antiarrhythmics produces *use-dependent* block. By blocking channels in the open or inactivated state, but not in the closed state, these agents preferentially affect cardiac tissue that is being frequently depolarized. These agents can, therefore, block high-frequency excitation of the myocardium (as might be seen in arrhythmias) while allowing for normal cardiac function.

Many of the antiarrhythmics have properties in multiple classes. For example, amiodarone is classified as Class III but also has some sodium-channel blocking action (Class I). Sotalol has both Class II and III properties.

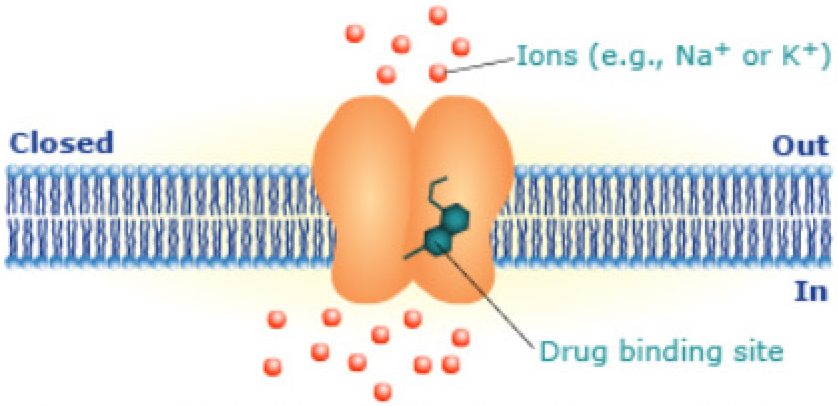
USMLE™ Key Concepts

For Step 1, you must be able to:

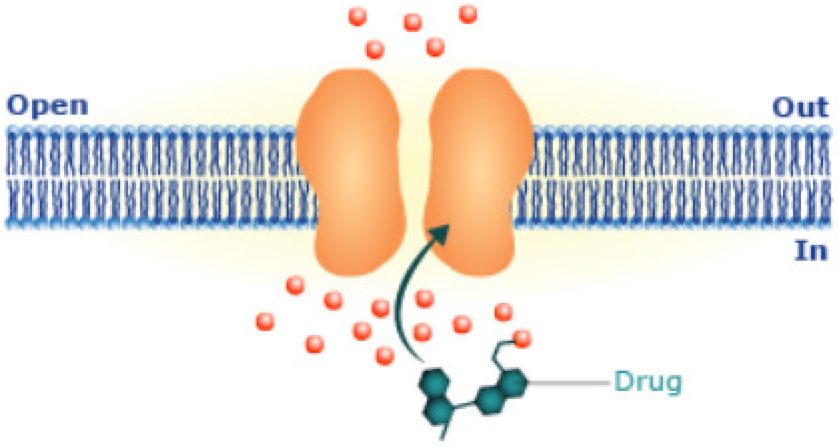
- Describe the mechanism of action, Vaughan Williams classification, therapeutic uses, and adverse effects of the commonly used antiarrhythmics.
- Explain the therapeutic approaches to the management of hypertension and the mechanism of action and adverse effects of antihypertensive agents.
- Identify the therapeutic approaches to management of angina and heart failure and the mechanism of action and adverse effects of these agents.
- Describe the treatment strategies for dyslipidemia and the mechanism of action and adverse effects of lipid-lowering drugs.
- Identify the mechanism of action and adverse effects of commonly used diuretics.


Closed Resting
(Recovery)
(Activation)
Closed Inactive
Open
(Inactivation)

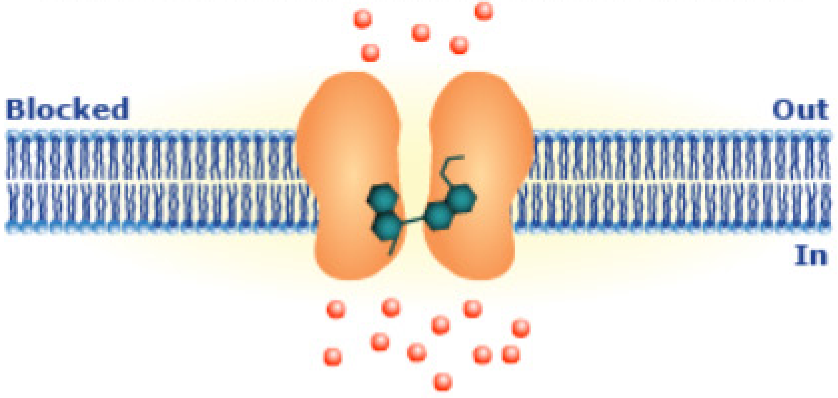
▲**Figure 3-1.2A** States of Ion Channel


Ions (e.g., Na⁺ or K⁺)
Closed
Out
In
Drug binding site

Drug unable to interact with channel in closed state


Open
Out
In
Drug

Drug binding site accessible in open state of channel


Blocked
Out
In

Channel blocked ("open-channel block")

▲**Figure 3-1.2B** Use-Dependent Block

1.2.1 Quinidine

Quinidine is now infrequently used except for some cases of atrial fibrillation and ventricular arrhythmias. It is available orally and has a half-life of six hours.

Quinidine may cause excessive prolongation of the QRS and QT intervals. The latter can be associated with the life-threatening arrhythmia torsade de pointes, which can progress to fatal ventricular fibrillation. Dose-dependent side effects of quinidine are collectively called cinconism from the derivation of quinidine from cinchona bark. They include:

- Tinnitus
- Vertigo, dizziness
- Headache
- Blurry vision
- Ocular changes (color changes, night blindness, scotomata)

Quinidine decreases the renal clearance of digoxin, enhancing digoxin toxicity (bradycardia, AV block, etc.) in patients on both medications.

1.2.2 Procainamide

Procainamide is only available intravenously in the United States. Use of procainamide is uncommon except for some atrial and ventricular arrhythmias. Procainamide is metabolized by N-acetyltransferase to N-acetylprocainamide (NAPA), an active metabolite.

Genetic variation in the activity of this enzyme (fast versus slow acetylators) influences toxic side effects, with slow acetylators being more prone to lupus-like adverse effects. Procainamide also may prolong the QT interval and lead to torsade de pointes.

1.2.3 Lidocaine

Lidocaine is only administered intravenously and is used for the treatment of ventricular arrhythmias, especially in the setting of myocardial ischemia (e.g., myocardial infarction). Lidocaine has very fast onset and offset. Lidocaine is heavily metabolized by the liver; rapid first-pass metabolism necessitates IV administration.

Dose-related CNS toxicity is one of the more common adverse effects. Less commonly, lidocaine also may cause bradycardia, hypotension, and arrhythmias.

1.2.4 Mexilitene

Mexilitene is similar to lidocaine in therapeutic effect for arrhythmias and is available orally.

1.2.5 Flecainide

Flecainide is given orally and is used to prevent refractory paroxysmal atrial fibrillation and to treat refractory ventricular tachycardia. Flecainide also is used as needed for the treatment of paroxysmal atrial fibrillation ("pill in the pocket").

Flecainide has had limited use since the CAST (Cardiac Arrhythmia Suppression Trial) study, which showed excess mortality in patients treated with flecainide following a myocardial infarction. Several related drugs have been taken off the market.

1.3 Class II: β-Adrenergic Receptor Blockers

Class II agents are β-adrenergic receptor antagonists (β-blockers) that blunt the sympathetic input into the heart. These agents are useful to prevent ventricular arrhythmias, especially after myocardial infarction. They also are used in supraventricular arrhythmias to reduce the frequency of episodes (e.g., paroxysmal supraventricular tachycardia) and control ventricular response (e.g., atrial fibrillation and atrial flutter).

They most commonly are given orally, although esmolol, a short-acting β-blocker, can be administered intravenously in the hospital setting. Sotalol has potassium-channel blocking action (Class III) in addition to β-blocker effects.

1.4 Class III: K^+ Channel Blockers

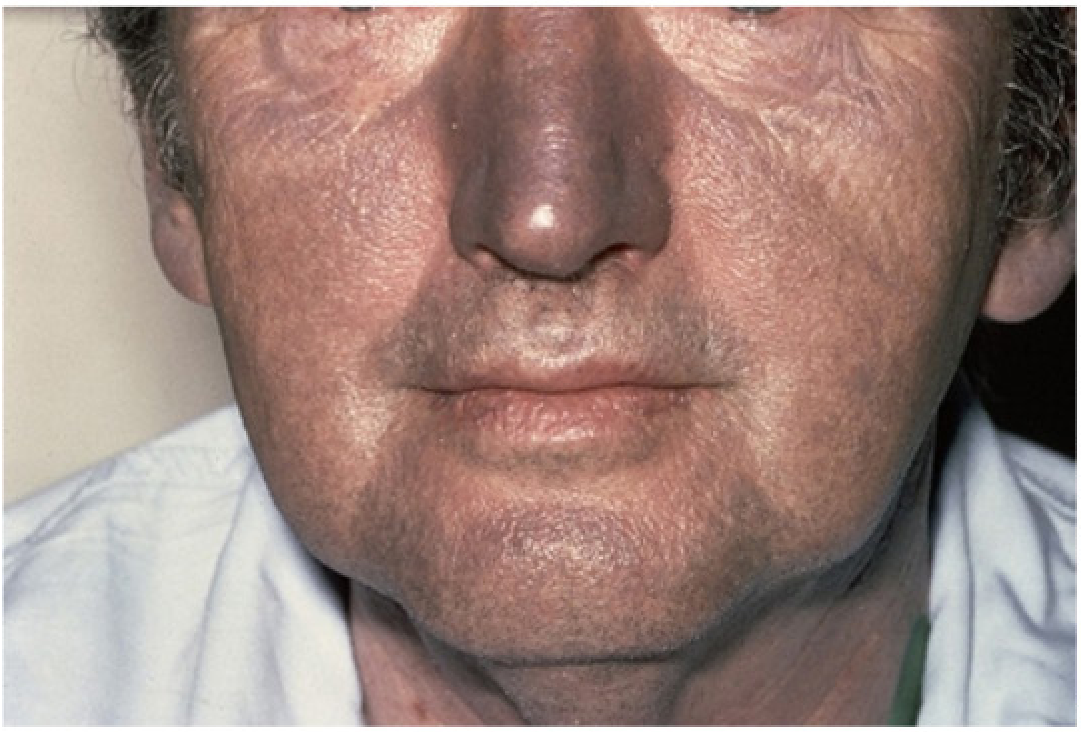
Class III agents predominantly block the delayed rectifier K current (IK_r) and thereby delay repolarization. The prototypical Class III agents include amiodarone, dofetilide, and ibutilide. Their action results in prolongation of the AP and ERP, which manifest as prolongation of the QT interval.

1.4.1 Amiodarone

Amiodarone is the most widely used antiarrhythmic overall and is effective against a wide range of atrial and ventricular arrhythmias. Amiodarone has a very long half-life and thus takes months to reach steady state.

Amiodarone has a number of adverse effects:

- Blue-gray discoloration of skin, especially sun-exposed regions
- Interference with clearance of digoxin, phenytoin, and warfarin
- Prolongation of QT interval and risk of torsade de pointes
- Pulmonary fibrosis
- Liver toxicity
- Thyroid dysfunction (contains iodine)

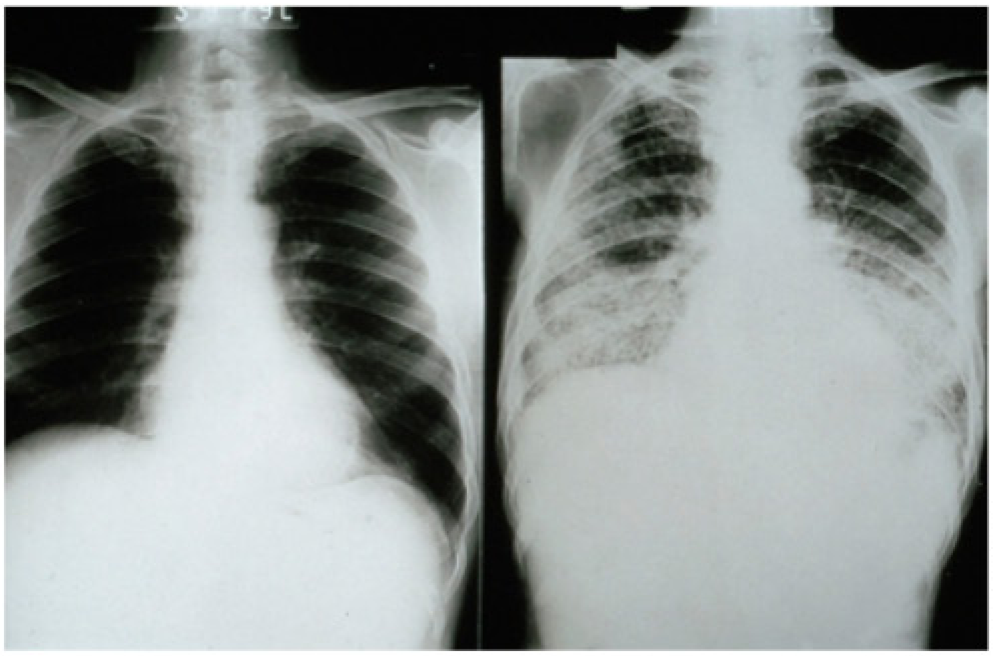


Wellcome Images/Custom Medical Stock Photo

▲**Figure 3-1.4A** Amiodarone-Induced Skin Changes

Important Concept

The adverse effects of amiodarone are very high yield. Pulmonary fibrosis is caused by a limited number of other drugs (e.g., bleomycin). The bluish skin discoloration is also uncommon to other drugs.



▲**Figure 3-1.4B** Chest X-Ray Showing Pulmonary Fibrosis

1.4.2 Dofetilide and Ibutilide

Dofetilide and ibutilide are used to convert atrial fibrillation and flutter to sinus rhythm. They are administered intravenously in the hospital setting.

1.5 Class IV: Ca^{2+} Channel Blockers

The prototypical Class IV agents are verapamil and diltiazem. These are non-dihydropyridine calcium channel blockers (contrasting with the dihydropyridines such as amlodipine and nifedipine used for blood pressure control). Verapamil and diltiazem preferentially antagonize calcium currents responsible for the depolarization phase in nodal tissue. Class IV agents are used in supraventricular arrhythmias to reduce the frequency of episodes (e.g., PSVT) and control ventricular response (e.g., atrial fibrillation and atrial flutter).

Adverse effects of verapamil and diltiazem include:

- Reduced blood pressure (especially orthostatic hypotension)
- Reduced cardiac output
- Lower extremity edema

1.6 Class V: Miscellaneous Antiarrhythmics

There are several antiarrhythmics that do not fit into the Class I-IV designations. These are not related to one another and are discussed individually.

1.6.1 Adenosine

Adenosine is a rapidly acting AV nodal blocker administered intravenously. The half-life of adenosine is only about 30 seconds and the drug effect fades rapidly after discontinuation of the drug. Adenosine activates G-protein-coupled adenosine receptors, which modulate potassium channels in the AV node. Adenosine is the drug of choice for stable paroxysmal supraventricular tachycardias (PSVTs).

Infusion of adenosine is often associated with shortness of breath, flushing, and a burning sensation in the chest.

1.6.2 Digoxin

Digoxin is discussed in more detail in the heart-failure section. Digoxin is used to control ventricular rates in atrial fibrillation and atrial flutter. Digoxin decreases the ventricular response by augmenting parasympathetic activity and slowing AV nodal conduction.

1.6.3 Electrolytes

Potassium and magnesium should be normalized in all patients with arrhythmias, especially ventricular tachycardia. Magnesium is specifically given to patients with polymorphic ventricular tachycardia in the setting of prolonged QT (torsade de points). Potassium also is given for digoxin toxicity-induced bradycardia (when hypokalemia is present).

2 Antihypertensives

Hypertension is a common problem that can lead to serious complications, such as stroke and kidney failure. Antihypertensive agents span a wide range of drug classes. Some drugs are widely used, such as the angiotensin-converting enzyme (ACE) inhibitors and diuretics, and others have more restricted uses.

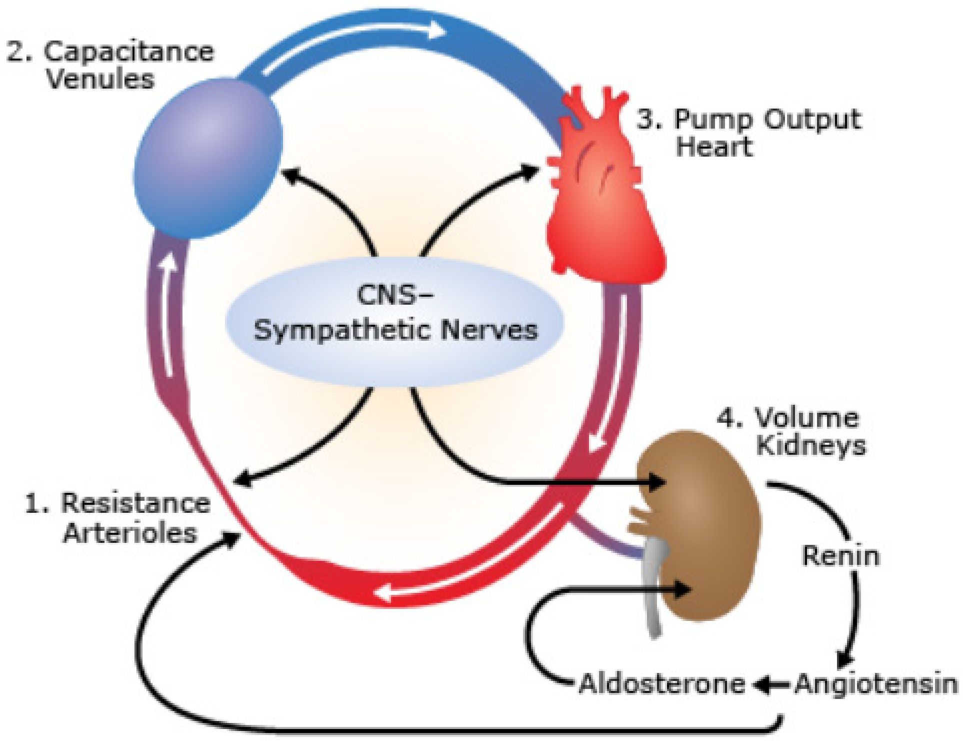
2.1 Overview

Each group of antihypertensive drugs has characteristic pharmacologic properties that target different factors underlying hypertension including increased sympathetic tone, increased renin-angiotensin activity, water/salt retention, and blood vessel tone. Most patients with hypertension have other medical problems, and antihypertensive therapy is often tailored based on co-morbid conditions. For example, the use of ACE inhibitors and angiotensin receptor blockers (ARBs) improves outcomes in patients with diabetes, renal disease, and heart failure. Similarly, β-blockers are beneficial in patients with ischemic heart disease.

▼**Table 3-2.1** Blood Pressure Classification

Classification of Blood Pressure			
Category	SBP mmHg		DBP mmHg
Normal	< 120	and	< 80
Prehypertension	120–139	or	80–89
Hypertension Stage 1	140–159		90–99
Hypertension Stage 2	≥ 160	and	≥ 100

Key: SBP = systolic blood pressure, DBP = distolic blood pressure
Source: U.S. Department of Health and Human Services, Washington, D.C.



▲**Figure 3-2.1** Regulation of Circulatory System

2.2 Diuretics

Diuretics (especially thiazide diuretics) are widely used to treat hypertension. Diuretics also are indicated for the treatment of fluid retention in congestive heart failure, edema (e.g., related to advanced renal or liver disease), and some electrolyte abnormalities. Major diuretic classes include: Thiazide diuretics, loop diuretics, potassium-sparing diuretics, osmotic diuretics, and carbonic anhydrase inhibitors. More detailed discussion of these agents appears at the end of this chapter.

2.3 Agents Acting on Central Sympathetic Nervous System

Prototypical centrally acting agents include α-methyldopa, clonidine, and reserpine. These agents modulate sympathetic output through effects in the central nervous system.

2.3.1 α-Methyldopa

α-Methyldopa is a prodrug that is converted to α-methylnorepinephrine. The active compound is an agonist at the presynaptic α_2-adrenoreceptors in the brainstem. This produces inhibition of CNS sympathetic outflow and a decrease in blood pressure (through decreases in in cardiac output and vascular tone).

α-Methyldopa has an excellent safety record in pregnancy and is the drug of choice for the treatment of mild to moderate hypertension in pregnancy.

Important Concept

Even though α-methyldopa is not commonly used, it is one of the drugs of choice for the management of mild to moderatate hypertension in pregnancy because of its excellent safety record.

The classic adverse effect of this agent is autoimmune (Coombs positive) hemolytic anemia. The Coombs test is used to detect the presence of auto-antibodies coating red blood cells (RBCs). The Coombs serum contains antibodies against human immunoglobulins. If the RBCs are coated with auto-antibodies, the RBCs will agglutinate (clump) in the presence of Coombs serum. Up to 20% of patients taking α-methyldopa will developed a positive Coombs test, but overt hemolytic anemia is rare.

Connection to Immunology

The direct Coombs test is used to diagnose IgG antibodies against red blood cells. It is performed by taking a sample of blood from the patient, adding antihuman globulin (Coombs serum) and observing for agglutination. The indirect Coombs test detects free antibodies in a patient's serum. It mixes the patient's serum with erythrocytes of known antigenicity, adding Coombs serum, and observing for agglutination.

2.3.2 Clonidine

Clonidine also activates presynaptic α_2-adrenoreceptors in the vasomotor center of the brainstem, reducing sympathetic output and decreasing blood pressure. Clonidine is not a first-line medication, and usually is given only if other medications fail.

Patients often experience a severe rebound syndrome marked by hypertension and tachycardia if the agent is abruptly stopped. The side effects markedly limit the use of clonidine.

Important Concept

Clonidine is classically associated with the most severe rebound hypertension of the commonly used antihypertensives.

2.3.3 Reserpine

Reserpine acts by irreversibly blocking the vesicular monoamine transporter (VMAT), which transports norepinephrine, dopamine, and serotonin from the cytoplasm of the presynaptic nerve terminal into storage vesicles for subsequent release. These neurotransmitters are then broken down. The net result is a depletion of neurotransmitters and reduced sympathetic outflow.

Reserpine can cause significant side effects, including sedation, major depression-like syndrome, and severe GI complications. This agent is rarely given because of side effects and relative ineffectiveness compared with newer agents.

2.4 Agents Acting on the Peripheral Sympathetic Nervous System

These agents act by modulating effects of the sympathetic nervous system peripherally. Prototypical members of this class include guanethidine, prazosin, and β-adrenergic receptor blockers.

2.4.1 Guanethidine

Guanethidine exerts its effects by acting as a "false neurotransmitter." It is transported across sympathetic nerve membranes by the norepinephrine transporter (NET) and concentrated into vesicles where it displaces norepinephrine. Because guanethidine is inactive at adrenergic receptors, the result is a decrease in sympathetic transmission.

Guanethidine can cause many adverse effects, including orthostatic hypotension and retrograde ejaculation (redirection of semen from the urethra into the urinary bladder due to decreased bladder sphincter tone).

Guanethidine is rarely used because of side effects and the advent of better agents.

2.4.2 α_1-Adrenergic Receptor Antagonists

Prototypical agents in this class include prazosin, doxazosin, and terazosin. These agents are selective antagonists of peripheral α_1-adrenergic receptors. They reduce blood pressure by relaxing vascular smooth muscle and decreasing arteriolar resistance.

α_1-receptor antagonists are uncommonly selected as primary agents to treat hypertension due to side effects such as orthostatic hypotension. Patients also may have a marked drop in blood pressure upon starting therapy leading to "first-dose syncope."

α_1-adrenergic antagonists may be considered in patients with benign prostatic hyperplasia (BPH) to prevent urinary retention. These drugs also have modest favorable effects on plasma lipids—decreased low-density lipoprotein (LDL) and increased high-density lipoprotein (HDL).

2.4.3 β-Adrenergic Receptor Antagonists (β-blockers)

β-blockers are widely used to treat hypertension. They often are more effective in younger patients due to higher resting sympathetic tone. The primary pharmacologic targets relevant for the treatment of hypertension are β_1-receptors in the heart and juxtaglomerular apparatus of the kidney. β_1 blockade results in decreased heart rate and contractility (i.e., β-blockers have negative chronotropic and negative inotropic effects).

Side effects associated with β-blockers include bradycardia, AV conduction block, hypotension, fatigue, and sexual dysfunction. β-blockers that cross the blood-brain barrier also may cause or exacerbate depression. The abrupt withdrawal of β-blockers may result in rebound hypertension and tachycardia. β-blockers with β_2 receptor affinity can result in bronchospasm, especially in those with underlying asthma (less so with COPD).

β-blockers should be avoided in patients with bradycardia (HR<55-60), AV block (>1st degree), or decompensated heart failure. First-line therapy for β-blocker overdose is intravenous glucagon, which binds to its receptor on cardiac cells and increases intracellular cAMP independently from the β-receptor.

▼**Table 3-2.4** Selectivity of β-Adrenoceptor Antagonists

Drug	Notes
Nonselective β-Adrenergic Antogonists	
Propanol Nadodol Timolol	Short half-life Long half-life Lipophilic-high CNS penetration
Nonselective β and α_1 Antogonists	
Labetalol Carvedilol	Also partial agonist at β_2-receptors Intermediate half-life
β-Adrenergic Partial Agonists	
Pindolol Acebutolol	β-nonselective β_1-selective
β_1-Selective Adrenergic Antagonists	
Esmolol Metoprolol Atenolol	Short-half-life (4 minutes) Intermediate half-life Intermediate half-life

Nonselective β-blockers These agents block both β_1- and β_2-receptors. Prototypical agents in this class include propranolol, nadolol, and timolol.

Although generally well tolerated, these agents are less frequently used for the treatment of hypertension because of the potential for pulmonary side effects (i.e., bronchospasm) related to β_2-receptor blockade and the availability of β_1 specific agents.

Nonselective β-blockers are indicated for other conditions, which, if present, may favor their use. For example, propranolol is effective for managing the sympathetic symptoms associated with hyperthyroidism as well as treating some anxiety/panic disorders. Both propranolol and nadolol are widely used for portal hypertension and cirrhosis. Timolol is formulated as an eye-drop for the treatment of glaucoma.

2.4.4 Nonselective β-blockers with α_1 Blocking Activity

This group contains agents that are nonselective β-blockers and possess α_1-receptor blocking activity. Prototypical drugs in this class include carvedilol and labetalol. The cardiac and renal effects of these agents is similar to other β-blockers; however, they also produce vasodilation and reduce peripheral vascular resistance through α_1 blockade on vascular smooth muscle. This property makes these agents considerably more effective as antihypertensives compared to other β-blockers. Labetalol, in particular, is commonly used for acute blood pressure control.

Labetalol is often chosen in treating cocaine overdose-related hypertension because α blockade prevents vasoconstriction by cocaine that can occur with other β-blockers due to "unopposed" α activity. Carvedilol is commonly given for chronic heart failure and has been shown to improve morbidity and mortality in this setting.

2.4.5 Cardio-Selective β-Blockers

These agents are selective for β_1-receptors and have minimal or no activity at β_2- and α_1-receptors. Prototypical drugs in this class include metoprolol, atenolol, and bisoprolol. The cardiac effect of these agents is similar to other β-blockers, but there is a much lower risk of pulmonary side effects.

Metoprolol is the most commonly prescribed β-blocker for hypertension. Multiple clinical trials show mortality and morbidity benefits with metoprolol in patients with chronic heart failure and post-myocardial infarction. Atenolol is an older medication but still used commonly because it is inexpensive and may be given once daily.

Esmolol is an intravenous β_1 selective agent with a very short half-life (~10 minutes) that is given as an intravenous bolus followed by a continuous infusion. Because of its short half-life, esmolol acts rapidly and can be titrated quickly.

Nebivolol is a relatively new selective β_1-blocker. It has a unique pharmacologic property in that it also increases the release of nitric oxide at the level of arterioles and thereby reduces peripheral resistance.

Important Concept

Be able to identify the classes into which the various β-blockers fall.

2.5 Direct Vasodilators

These drugs act directly on the arteriolar smooth muscle, causing a decrease in systemic vascular resistance and lowering of blood pressure. Prototypical agents in this class include hydralazine, nitroprusside, and minoxidil.

2.5.1 Hydralazine

Hydralazine is a short-acting agent that likely acts by increasing the production of cGMP and ultimately nitric oxide. It often is used intravenously for short-term treatment of moderate to severe hypertension. Hydralazine is safe in pregnancy, and may be used to control hypertension in this setting.

Important Concept

Hydralazine is the drug of choice for managing severe hypertension in pregnancy.

Hydralazine is generally well tolerated but may cause symptoms related to vasodilation, including orthostatic hypotension, headache, flushing, and sweating. The classic side effect associated with hydralazine is a systemic, lupus-like syndrome which is more common in "slow acetylators" with low N-acetyltransferase activity.

2.5.2 Sodium Nitroprusside

Sodium nitroprusside is an intravenous medication used for hypertensive emergencies. Nitroprusside is metabolized to nitric oxide and causes venous and arterial vasodilation through cGMP dependent pathways. Nitroprusside causes rapid reduction in preload (venodilation) and afterload (arterial vasodilation) and can be rapidly titrated.

Nitroprusside is a potent antihypertensive, and hypotension can occur due to excessive vasodilatation. Nitroprusside is converted to cyanide and thiocyanate ions in vivo and may cause cyanide toxicity when administered at higher doses for more than 72 hours. Sodium nitrite followed by sodium thiosulfate is the antidote to cyanide poisoning and may be administered if toxicity is suspected.

2.5.3 Minoxidil

Minoxidil is a potent direct arteriolar vasodilator that is available orally and usually reserved for refractory hypertension. Minoxidil acts to open potassium channels in vascular smooth muscle, causing hyperpolarization of the cellular membrane. This leads to smooth muscle relaxation, reduced peripheral vascular resistance, and decreased blood pressure.

The most common side effects are hypotension, salt retention, and edema. Minoxidil also can cause the side effect of hypertrichosis (excess hair growth), which has been exploited in topical hair products for baldness (e.g., Rogaine).

2.6 Calcium Channel Antagonists

There are two classes of calcium channel antagonists or calcium channel blockers (CCBs) called the "dihydropyridines" (DHP) and "non-dihydropyridines" (non-DHP), respectively.

2.6.1 Dihydropyridine Calcium Channel Blockers

The DHP class of CCBs is more commonly used in the treatment of hypertension and includes agents such as nifedipine, amlodipine, felodipine, and nisoldipine. These agents block L-type calcium channels in vascular smooth muscle, causing vasodilation and decreased peripheral vascular resistance. They do not strongly affect cardiac tissue channels and have no effects on heart rate or contractility. The most common side effects of DHP calcium channel blockers are hypotension and lower extremity edema.

2.6.2 Non-dihydropyridine Calcium Channel Blockers

The non-DHP class of CCBs is used less commonly for the treatment of hypertension and included verapamil and diltiazem. These drugs antagonize calcium channels in the heart resulting in decreased heart rate and contractility. They also significantly slow AV nodal conduction. They may be used to control hypertension in patients with angina who cannot tolerate β-blockers. Adverse effects of non-DHP agents include edema and AV conduction block.

2.7 Agents Modulating the Renin-Angiotensin-Aldosterone System

Two main classes of drugs affect the renin-angiotension-aldosterone system: The angiotensin coverting enzyme (ACE) inhibitors and angiotension II receptor antagonists (ARBs). Both classes of drugs are widely used and have shown substantial clinical effect. A more recent addition to the therapeutic options for hypertension are the renin inhibitors, such as aliskerin.

2.7.1 Angiotensin Converting Enzyme (ACE) Inhibitors

ACE inhibitors are a widely used class of agents for the treatment of hypertension and include drugs such as enalapril, captopril, lisinopril, and ramipril. All agents are effective, and differences are mostly related to pharmacokinetic properties such as half-life and dosing interval. Multiple clinical trials have demonstrated long-term benefits of ACE inhibitors in patients with a range of conditions including left ventricular systolic dysfunction (especially post-myocardial infarction), diabetic or hypertensive nephropathy, heart failure, and stroke. ACE inhibitors have been shown to have positive effects on preventing pathologic cardiac remodeling following myocardial infarction and can prevent cardiac dilatation and worsening of heart failure.

ACE inhibitors prevent the conversion of angiotensin I to angiotensin II by ACE, thereby attenuating the vasoconstrictive effects of angiotensin II peripherally (afterload reduction) and in the kidney (causing efferent arteriolar dilation). They also decrease the release of aldosterone into blood (angiotensin II normally stimulates the release of aldosterone) preventing sodium and water retention. ACE also is responsible for the breakdown of bradykinin (a vasodilator), and ACE inhibitors result in an accumulation of bradykinin, which may have beneficial vasodilatory effects but may also contribute to side effects (see following).

2.7.2 Angiotensin II Receptor Antagonists (ARBs)

ARBs also are commonly used in the treatment of hypertension. Prototypical agents in this class include candesartan, irbesartan, losartan, and valsartan. These drugs directly antagonize the angiotensin II receptor, and thereby blunt its vasoconstrictive effects. Unlike ACE inhibitors, they do not affect bradykinin metabolism. ARBs have similar effectiveness to ACE inhibitors in regard to blood pressure control, but it is less clear if these drugs possess all the long-term benefits shown with ACE inhibitors.

2.7.3 Adverse Effects of ACE Inhibitors and ARBs

Both ACE inhibitors and ARBs can cause hypotension, decreased renal function, and hyperkalemia. Alterations in renal function are the result of a combination of decreased blood pressure and decreased glomerular filtration due to efferent arteriolar dilation. This effect is accentuated in patients with renal artery stenosis (RAS), and these agents are contraindicated in bilateral RAS (or in patients who only have a single functioning kidney with RAS). Heavy NSAID use increases the risk of adverse renal effects related to the use of ACE inhibitors and ARBs.

Both ACE inhibitors and ARBs are contraindicated throughout pregnancy because of detrimental effects on fetal renal function (e.g., oligohydramnios and Potter syndrome) and possible teratogenicity.

Some side effects are seen much more commonly with ACE inhibitors than ARBs, and are likely related to inhibition of bradykinin metabolism by blocking the activity of ACE. Most notable is a persistent dry cough, which usually develops shortly after ACE inhibitor initiation. This usually is managed by changing the patient to an ARB. A more serious, though rare, reaction associated with ACE inhibitors is life-threatening angioedema, an adverse reaction that resembles anaphylaxis and that may be related to inhibition of bradykinin metabolism.

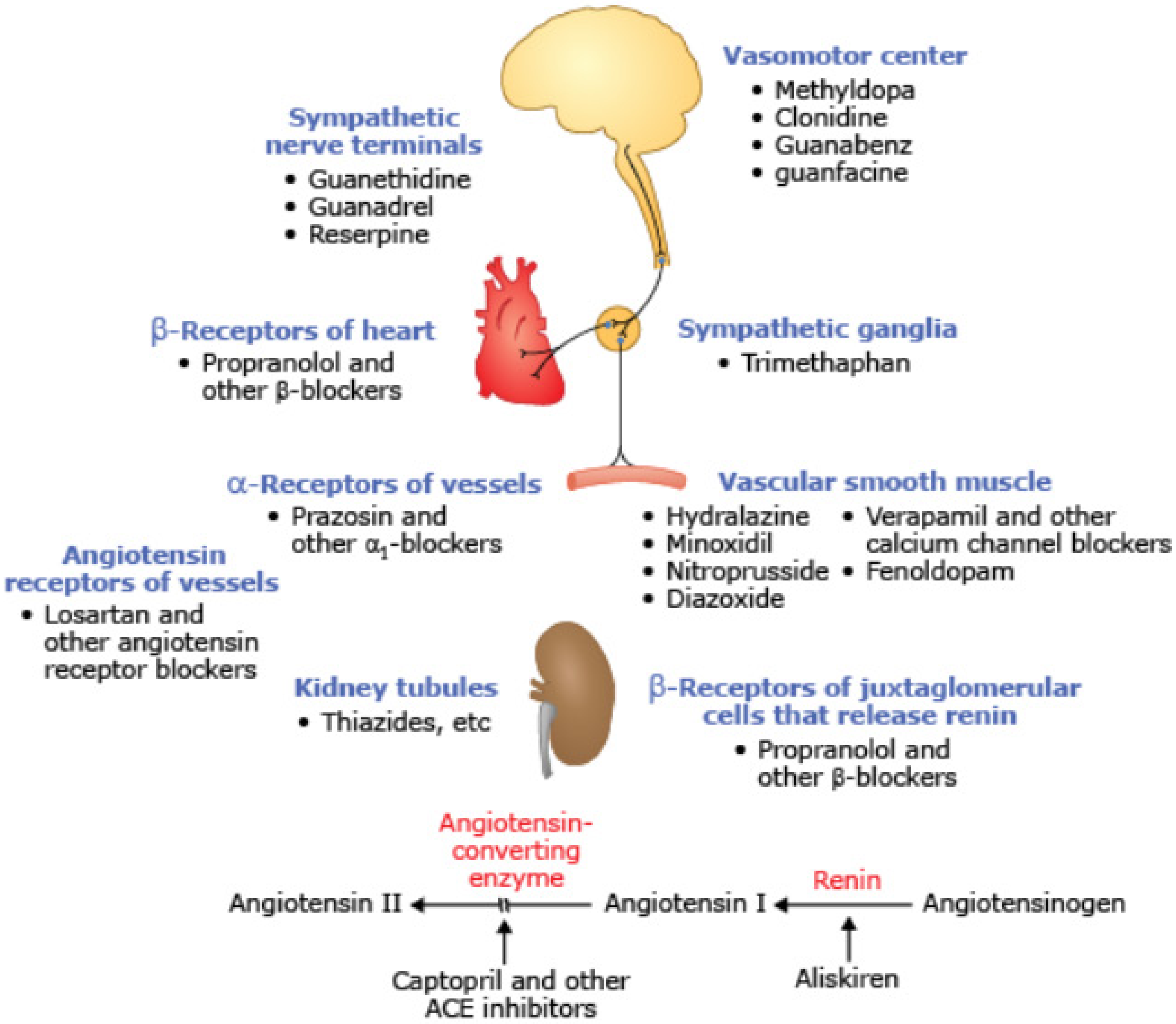
2.7.4 Renin Inhibitors

This is a newer class of antihypertensive agents, which act by directly inhibiting the enzyme renin and thus blocking the conversion of angiotensinogen to angiotensin I. The principle member of this class is aliskerin, which appears to be effective for the treatment of hypertension.

The adverse effects of aliskerin resemble those of ACE inhibitors and include cough, hyperkalemia, and rare cases of angioedema.

Important Concept

Be able to identify the adverse effects of ACE inhibitors and ARBs, and which adverse effects are seen more with ACE inhibitors than ARBs (e.g., cough).


Vasomotor center
• Methyldopa
• Clonidine
• Guanabenz
• guanfacine
Sympathetic nerve terminals
• Guanethidine
• Guanadrel
• Reserpine
β-Receptors of heart
• Propranolol and other β-blockers
Sympathetic ganglia
• Trimethaphan
α-Receptors of vessels
• Prazosin and other α_1-blockers
Vascular smooth muscle
• Hydralazine
• Minoxidil
• Nitroprusside
• Diazoxide
• Verapamil and other calcium channel blockers
• Fenoldopam
Angiotensin receptors of vessels
• Losartan and other angiotensin receptor blockers
Kidney tubules
• Thiazides, etc
β-Receptors of juxtaglomerular cells that release renin
• Propranolol and other β-blockers
Angiotensin-converting enzyme
Angiotensin II
Angiotensin I
Renin
Angiotensinogen
Captopril and other ACE inhibitors
Aliskiren

▲**Figure 3-2.7** Hypertensive Drugs: Sites of Action

3 Drugs for Heart Failure

There are a variety of drugs used for the management of heart failure. Some are for chronic management and others are used for acute heart failure exacerbations. During the last decade, the use of ACE inhibitors and ARBs have become very common while the use of digoxin has faded.

3.1 ACE Inhibitors and Angiotensin II Receptor Antagonists

ACE inhibitors and ARBs are first-line agents for patients with heart failure, especially those with reduced systolic function (to date, no class of drug has been conclusively shown to improve mortality in heart failure with preserved systolic function). Patients with heart failure should receive either an ACE inhibitor or an ARB unless there is a clear contraindication to use of these drugs. Both classes of drugs slow disease progression and improve mortality in heart failure. These agents reduce preload (venodilation) and afterload (arterial dilation) and may improve cardiac output, but should not be used in patients who are hypotensive.

ACE inhibitors and ARBs also are standard therapy following myocardial infarction. They are especially important for patients with reduced systolic function. ACE inhibitors and ARBs can help prevent negative remodeling that leads to heart failure after myocardial infarction.

3.2 Cardiac Glycosides (Digoxin)

This class of drugs was once the dominant group of drugs used for the management of heart failure. However, adverse effects and the advent of other drugs, such as ACE inhibitors, have led to the declining use of cardiac glycosides. Unlike ACE inhibitors and ARBs, there is no clear evidence that cardiac glycosides improve survival, although they do improve patient symptoms and lifestyle. The only cardiac glycoside currently used in the United States is digoxin.

3.2.1 Mechanism of Action

Digoxin works by inhibiting the Na^+/K^+ ATPase pump. Normally, the Na^+/K^+ ATPase pumps Na^+ out of the cell and K^+ ions into the cell. When this process is disrupted, the intracellular Na^+ concentration increases, reducing the driving force for Ca^{2+} efflux by the Na^+/Ca^{2+} antiporter, which normally pumps Ca^{2+} out of the cell and Na^+ back in. This leads to an accumulation of Ca^{2+} intracellularly that is taken up by the sarcoplasmic reticulum. The end result is more Ca^{2+} available for release by the sarcoplasmic reticulum in response to depolarization, increasing the force of contraction.

3.2.2 Interaction of Digoxin With Potassium Ions

Digoxin binds to the Na^+/K^+ ATPase at the potassium ion binding site, and competes with extracellular potassium ions for binding at that location. Hyperkalemia decreases effects of digoxin, because K^+ displaces digoxin from the target ATPase. Conversely, hypokalemia increases digoxin's effects and may lead to or worsen toxicity, because digoxin can bind the ATPase more strongly without the presence of K^+. Serum potassium levels should be kept in the normal range in patients taking digoxin.

3.2.3 Adverse Effects

Digoxin has a narrow therapeutic index and frequently causes adverse effects. Signs of toxicity include gastrointestinal symptoms (such as anorexia and nausea), neurologic changes (confusion, hallucinations), visual disturbances (yellow-green auras or halos), and electrolyte abnormalities. Symptoms also vary depending on whether toxicity is acute or chronic. Patients with acute toxicity tend be more acutely ill, while chronic toxicity is more insidious.

The most life-threatening adverse effects are cardiac, which can present with almost any arrhythmia, including premature ventricular contractions, bradycardia, atrial tachyarrhythmias with AV block, ventricular bigeminy, junctional rhythms, ventricular tachycardia, and ventricular fibrillation. The so-called classic digoxin effect on the ECG consists of T wave changes (flattening or inversion), QT interval shortening, and scooped ST segments with ST depression. The digoxin effect is commonly seen and does not signify toxicity.

3.2.4 Management of Digoxin Toxicity

Supportive care and treatment of arrhythmias are the cornerstone of toxicity management. Electrolytes, especially K^+ and Mg^{2+}, should be adjusted to normal levels while waiting for digoxin levels to decrease. In critically ill patients, especially those with acute toxicity, antidigoxin immunotherapy can be given. This consists of digoxin-specific Fab fragments (e.g., DigiFab), which bind digoxin and remove it from plasma. Antidigoxin immunotherapy is usually effective but is quite expensive (> $5,000).

3.2.5 Drug Interactions With Digoxin

Digoxin has important interactions with a number of drugs. Classic examples are quinidine and furosemide. Quinidine alters digoxin binding in body tissues, resulting in higher effective digoxin concentrations in cardiac tissue, and also slows renal clearance of digoxin. These two effects result in a markedly increased risk for toxicity.

Furosemide and thiazide diuretics, however, can enhance digoxin effects by producing hypokalemia. Drugs such as amiodarone, erythromycin, and verapamil increase digoxin levels, although the specific mechanisms are unknown.

3.3 Diuretics

Patients with chronic heart failure often are on daily diuretic therapy to control volume retention and congestive symptoms. There is no direct evidence that diuretics improve mortality in heart failure. The most commonly used drugs are loop diuretics (e.g., furosemide, bumetanide, and torsemide). Some patients require combinations of a loop diuretic with a thiazide diuretic, such as metolazone or hydrochlorothiazide. Because these drugs act on different portions of the nephron, they can be very effective in combination.

In addition to improving symptoms, diuretics reduce preload, decrease heart stress, and improve cardiac performance. Acute heart failure exacerbations usually require intravenous loop diuretic therapy (furosemide or bumetanide) to remove volume quickly. Recent trials show that bolus injections and continuous infusions of the loop diuretics are clinically equivalent.

Side effects of diuretic therapy include electrolyte depletion, especially potassium and magnesium, hypovolemia, worsening renal function, and metabolic alkalosis ("contraction alkalosis").

3.4 β-Blockers

β-blockers are used frequently in the treatment of chronic heart failure. Carvedilol, metoprolol, and bisoprolol have all been shown to improve mortality in chronic congestive heart failure. These patients have elevated sympathetic tone, which contributes to negative myocardial remodeling. β-blockers help prevent this remodeling. However, because of their negative inotropic effects, caution must be used to prevent hypotension and decompensation. β-blockers are beneficial when used chronically in heart failure and should not be started or up-titrated during acute exacerbations (occasionally β-blockers need to be stopped or down-titrated).

3.5 Vasodilators

Patients with congestive heart failure often have very high peripheral vascular resistance. Arterial vasodilators can reduce afterload and improve cardiac output in patients with heart failure. The most commonly used arterial dilator is hydralazine.

Long-acting nitrates, such as isosorbide mononitrate and isosorbide dinitrate, have some arterial dilating properties but are primarily venodilators and act by reducing preload. Nitrates are especially useful if there is coexisting angina. Most commonly, nitrates and hydralazine are used together in patients with systolic heart failure who remain symptomatic while receiving maximal medical therapy, including ACE inhibitors, β-blockers, and diuretics. The strongest data is for use in African-American patients, but use in other ethnic groups is probably reasonable.

3.6 Treatment of Cardiac Shock

Cardiogenic shock is a condition in which there is insufficient systemic perfusion due to cardiac pump failure. This is most commonly the result of end-stage cardiomyopathy or as a complication of myocardial infarction. Cardiogenic shock is characterized by decreased cardiac output, increased peripheral vascular resistance, and increased left ventricular end diastolic volume (high wedge pressure). Treatment of cardiogenic shock is directed toward correcting these abnormalities.

3.6.1 β-Adrenergic Agonists

β-adrenergic agonists increase cardiac output by acting on cardiac β_1-receptors. These agents have both positive inotropic and chronotropic effects. In cardiogenic shock, they are primarily used for their inotropic properties.

Dobutamine This is a selective β_1 agonist (very little activity at β_2-receptors) that is used frequently in cardiogenic shock. Dobutamine is only given intravenously and is commonly used for severely decompensated heart failure in the hospital setting, including as a bridge to cardiac transplantation. The chronic use of inotropes does not improve mortality and may be detrimental because of arrhythmogenic properties.

Dopamine This agent is a catecholamine that also is used for cardiogenic shock, although less frequently than dobutamine. Dopamine is given intravenously and has complex, dose-dependent pharmacology. At low doses (2–5 µg/kg/min), dopamine will increase renal perfusion through the dopamine-1 receptors in the kidney and may modestly assist diuresis. At medium doses (3–5 µg/kg/min), there is an increase in cardiac output through agonism of the cardiac β_1 receptor. These are the doses typically used for cardiogenic shock.

High doses (5–10 µg/kg/min) activate peripheral α_1-receptors and cause vasoconstriction, an often undesirable effect in cardiogenic shock. Because dopamine can increase cardiac output and systemic vascular resistance, it also is used for other types of shock (e.g., septic shock).

Isoproterenol This is an intravenous β_1-/β_2-adrenergic agonist that is used primarily for symptomatic bradycardia because of its chronotropic properties. Isoproterenol mainly increases heart rate but also has some effects on contractility.

Isoproterenol use should be avoided in patients with myocardial ischemia due to increased myocardial oxygen demand. Isoproterenol also may precipitate or worsen ventricular tachyarrhythmias.

3.6.2 Phosphodiesterase Inhibitors

Phosphodiesterase-3 (PDE_3) inhibitors are inotropic agents that act by preventing the breakdown of cyclic AMP (cAMP) in the cytosol of cardiac myocytes. Normally, cAMP is increased by activation of the β_1-receptor; therefore PDE3 inhibitors act "downstream" of the β_1-receptor.

Milrinone and amrinone are PDE_3 inhibitors used in cardiogenic shock in a similar fashion to dobutamine. In addition to increasing inotropy, these agents have vasodilitory properties in the pulmonary and systemic vasculature and reduce right ventricular and left ventricular afterload. Milrinone is more commonly used than amrinone.

3.6.3 Nitroprusside

Nitroprusside, as discussed previously, is a potent venodilator and arterial dilator. In the setting of cardiogenic shock, this agent can improve cardiac output by reducing preload and afterload. Paradoxically, nitroprusside may increase blood pressure in these patients by increasing cardiac output, though excessive vasodilation also may cause hypotension.

3.6.4 Diuretics

Diuretics are used to treat pulmonary congestion and optimize volume status in cardiogenic shock.

4 Treatment of Angina Pectoris

Angina is chest pain or discomfort caused by myocardial ischemia. Angina is the result of an imbalance between myocardial oxygen supply and demand.

4.1 Antianginal Agents

A number of classes of agents are used in the management of angina, including nitrates, non-dihydropyridine calcium channel antagonists, β-adrenergic receptor antagonists, and a special class of Na^+ channel antagonists with a single member at present (ranolazine).

4.1.1 Goal of Treatment

The therapeutic aim in angina management is:

- Decrease oxygen demand by decreasing heart rate, contractility, afterload, and preload.
- Increase oxygen supply by promoting coronary blood flow.

4.1.2 Nitrates

Nitrates are the most commonly used agents for the management of angina. Acute angina, as in the setting of an acute coronary syndrome, is treated with short-acting agents, usually nitroglycerin administered intravenously or as a sublingual tablet or buccal spray (note: sublingual administration bypasses the portal circulation and avoids first-pass metabolism by liver). Amyl nitrite is a short-acting agent that is much less commonly used.

Chronic angina, as in stable coronary artery disease, is treated with long-acting drugs such as oral formulations of isosorbide mononitrate and dinitrate. Nitroglycerin as a sustained release patch also may be used to treat chronic angina.

Mechanism of Action Nitrates are converted in cells to nitric oxide (NO). Nitric oxide, in turn, is an activator of guanylyl cyclase which results in generation of cGMP. Cyclic GMP then activates myosin light chain phosphatase via a cGMP-dependent protein kinase resulting in vasodilation.

- The major action of nitrates in the treatment of angina results from venodilation and decreased venous return, which reduces end-diastolic volume (i.e., reduced preload). The result is decreased cardiac wall stress and oxygen demand, bringing the balance between oxygen consumption and demand into balance.
- Nitrates also cause dilation of coronary arteries, leading to improved oxygen supply to cardiac muscle. However, this is a minor contributor to the antianginal effects of these agents.

Tachyphylaxis This describes the phenomenon of decreased response with repeated dosing of a drug. If given continuously, nitrates lose their effectiveness over time. To avoid tachyphylaxis, patients should have a nitrate-free interval of 8–12 hours or more during their dosing cycle to restore effectiveness.

Adverse Effects Nitrates can cause excessive vasodilation, including flushing, throbbing headache (common), orthostatic hypotension, syncope, and reflex tachycardia.

Nitrates have a well-publicized drug-drug interaction ("If you take nitrates for chest pain . . . ") with the phosphodiesterase-5 (PDE_5) inhibitors used for the treatment of erectile dysfunction (sildenafil, tadalafil, vordenafil). PDE_5 inhibitors inhibit the degradation of cGMP in erectile tissue, and thereby promote vasodilation. However, PDE_5 inhibitors also have some systemic vasodilatory effects. The combination of nitrates and PDE5 inhibitors has led to sudden deaths attributed to excessive hypotension.

4.1.3 Calcium Channel Blockers

Both dihydropyridine and non-dihydropyridine CCBs can be used for prevention of angina. Non-dihydropyridines (diltiazem and verapamil) reduce heart rate and contractility, decreasing myocardial oxygen demand. Dihydropyridines (nifedipine and amlodipine) mainly work by lowering blood pressure, afterload, and cardiac work. These agents also dilate coronary arterioles and improve myocardial perfusion.

Dihydropyridines also may cause a reflex tachycardia and paradoxically increase oxygen demand.

4.1.4 β-Blockers

β-blockers, especially cardioselective agents such as metoprolol, are very effective for the treatment of angina and are commonly used for this indication. These drugs decrease heart rate, blood pressure, inotropy, and cardiac work, and thereby reduce myocardia oxygen demand.

4.1.5 Ranolazine

Ranolazine is a newer antianginal agent that blocks late Na^+ influx into cardiac myocytes during repolarization. This activity has a secondary effect of reducing calcium influx via the sodium-calcium exchanger. By attenuating calcium overload, ranolazine promotes cardiac relaxation and decreases wall stress. This agent is generally added when angina is refractory to other therapies.

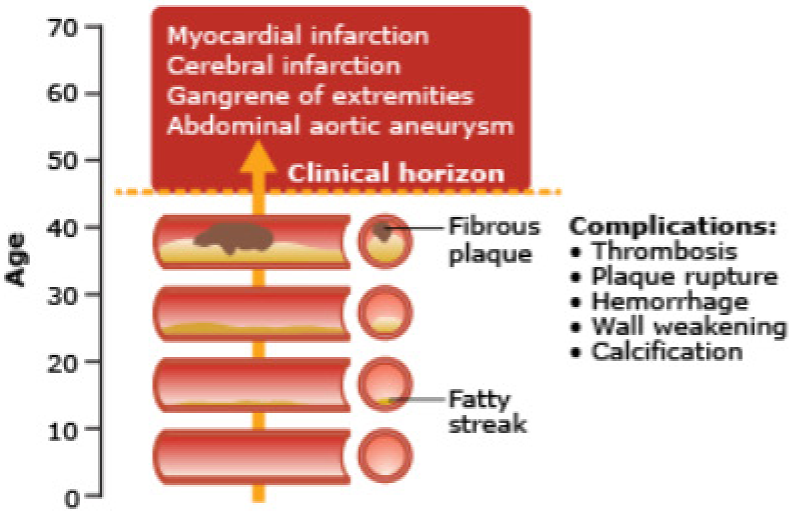
Ranolazine also inhibits outward potassium channels and may prolong the QT interval.

5 Antihyperlipidemics

Dyslipidemia is a major risk factor for a wide range of clinical disorders, most commonly affecting the cardiovascular system. Various drugs are available to improve lipid profile and thereby reduce the risk of cardiovascular complications.

5.1 Overview of Plasma Lipid Abnormalities

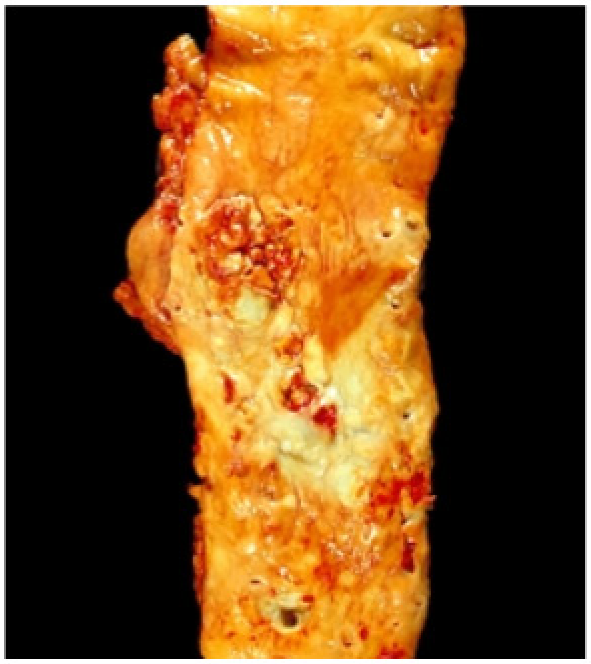
Dyslipidemia can manifest in a variety of clinical signs and symptoms. Plasma lipid profile is often measured to assess the risk for cardiovascular disease.


70
60
50
40
30
20
10
0
Age
Myocardial infarction
Cerebral infarction
Gangrene of extremities
Abdominal aortic aneurysm
Clinical horizon
Fibrous plaque
Fatty streak
Complications:
• Thrombosis
• Plaque rupture
• Hemorrhage
• Wall weakening
• Calcification

▲ **Figure 3-5.1A** Atherosclerosis and Thrombosis

5.1.1 Atherosclerosis

Atherosclerosis refers to a condition in which artery walls thicken due to the accumulation of lipid deposits. There is a secondary inflammatory response in the walls of arteries, caused by the accumulation of inflammatory cells, such as macrophages. This process is promoted by elevated levels of low-density lipoprotein (LDL).



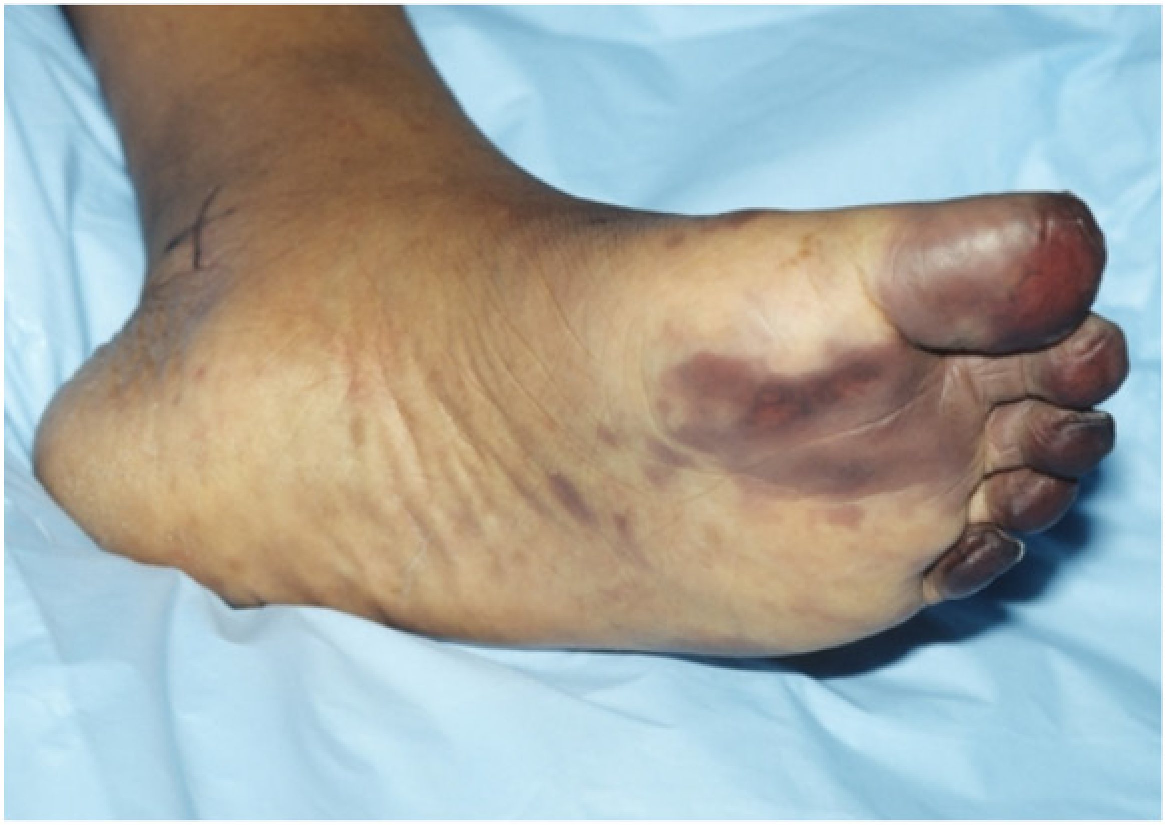
Science Source

▲ **Figure 3-5.1B** Lipid Deposits on Artery Walls

Coronary Artery Disease In coronary arteries, plaques may narrow the caliber of vessels, leading to decreased oxygen delivery and stable angina. Atherosclerotic plaques also may result in acute coronary syndromes through rupture, secondary thrombus formation, or an acute reduction of blood flow.

Peripheral Vascular Disease In peripheral arteries, atherosclerosis may critically reduce blood flow to organs or limbs such as in renal artery stenosis, intermittent claudication, and ischemic foot ulcerations. Atheromatous plaques in large vessels such as the aorta may embolize debris distally, resulting in digital necrosis and acute limb ischemia.

Cerebral Vascular Accidents Atheromatous plaques in carotid arteries also may embolize debris distally to the cerebral vasculature, resulting in embolic strokes.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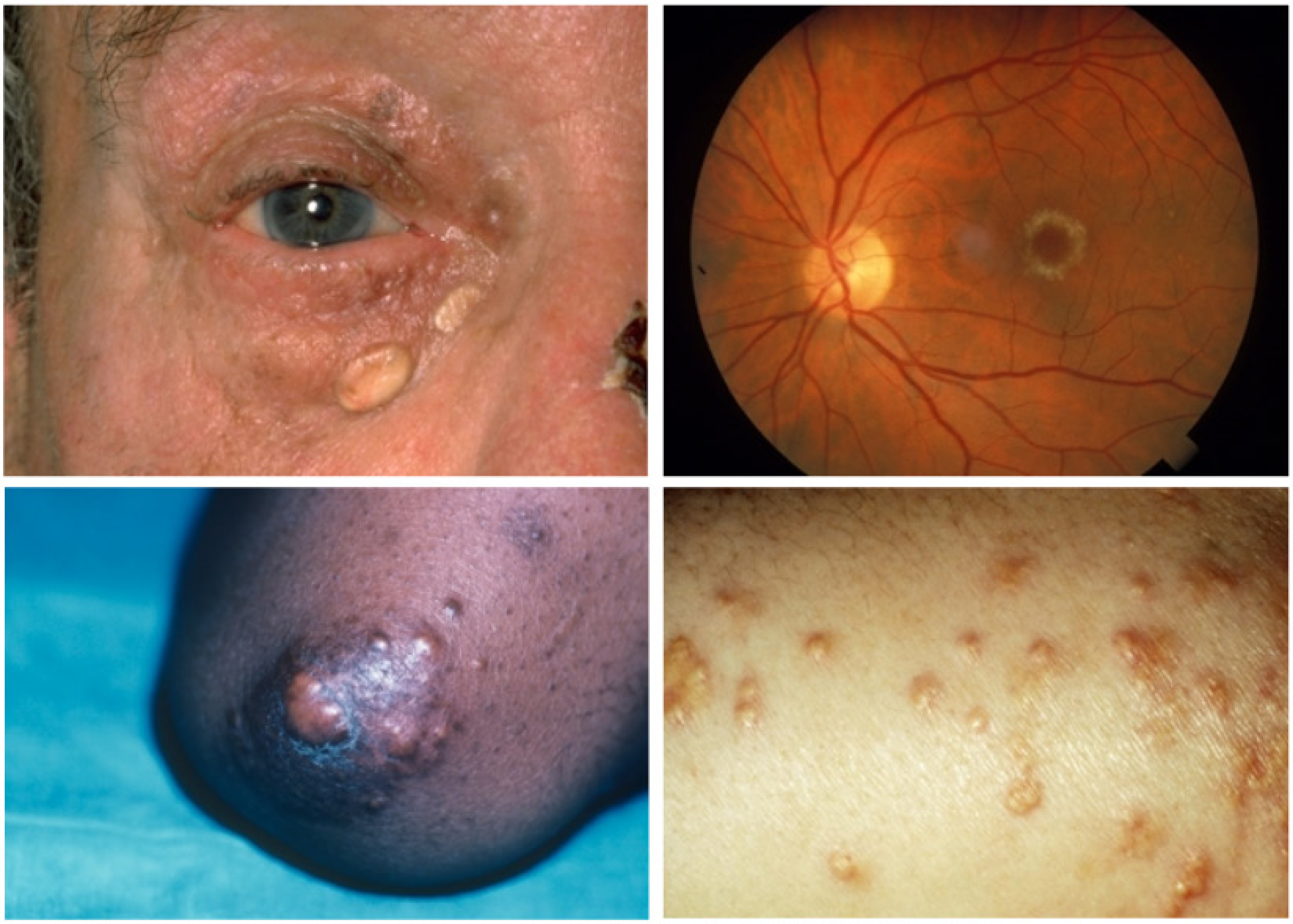
▲**Figure 3-5.1C** Atheroembolism

5.1.2 Cholesterol Gallstones

Cholesterol gallstones form when bile contains too much cholesterol and not enough bile salts.

5.1.3 Visible Manifestations of Hyperlipidemia

Extreme hyperlipidemia may have visible manifestations including xanthelasma, retinal lipid deposits, tendon xanthomas, and skin xanthomas.



(tl) Mediscan/Visuals Unlimited, Inc.; (tr) Barbara Galati/Phototake, Inc.; (bl) Dr. Ken Greer/Visuals Unlimited, Inc.; (br) Biophoto Associates/Sciene Source

▲ **Figure 3-5.1D** Manifestations of Hyperlipidemia

5.1.4 Goals of Antilipidemic Therapy

The primary goal of therapy is reduction of LDL cholesterol. Once LDL is at the goal, then other lipids can be addressed. The only exception is for patients with very high triglycerides (>500 mg/dL), where the goal is to prevent pancreatitis by lowering triglyceride levels. All patients should be encouraged to initiate therapeutic lifestyle changes, including a low-fat diet, weight loss, and increased physical activity.

Low-Density Lipoprotein (LDL) Target LDL is based on coronary heart disease (CHD) risk, with patients in higher-risk categories having more aggressive (i.e., lower) LDL goals. Risk is determined by assessing the absolute 10-year risk of CHD using the Framingham Risk Score and the presence of CHD risk factors (smoking, hypertension, HDL <40 mg/dL, age ≥45 in men and ≥55 in women, family history of premature CHD in a first-degree relative):

- **High risk** (established CHD, "CHD equivalent," including diabetes, abdominal aortic aneurysm, peripheral vascular disease, carotid artery disease, or 10-year risk >20%): Goal LDL <100 mg/dL and optimally <70 mg/dL.
- **Intermediate high risk** (2+ risk factors and 10-year risk 10%–20%): Goal LDL <130 mg/dL and optimal <100 mg/dL.
- **Intermediate low risk** (2+ risk factors and 10-year risk <10%): Goal LDL <130 mg/dL.
- **Low risk** (0–1 risk factors; 10-year risk not needed): Goal LDL <160 mg/dL.

High-Density Lipoprotein (HDL) HDL participates in reverse cholesterol transport and is protective against CHD. Very high HDL (>60 mg/dL) is a "negative risk factor" and low HDL (<40 mg/dL) is a predictor of CHD. There is not a specific goal for raising HDL.

Triglycerides As mentioned previously, triglycerides are a primary target of therapy if they are >500 mg/dL. The initial aim is to prevent acute pancreatitis through triglyceride lowering by using very low-fat diets, weight reduction, increased physical activity, and a triglyceride-lowering drug (fibrate or nicotinic acid).

5.2 Antihyperlipidemics

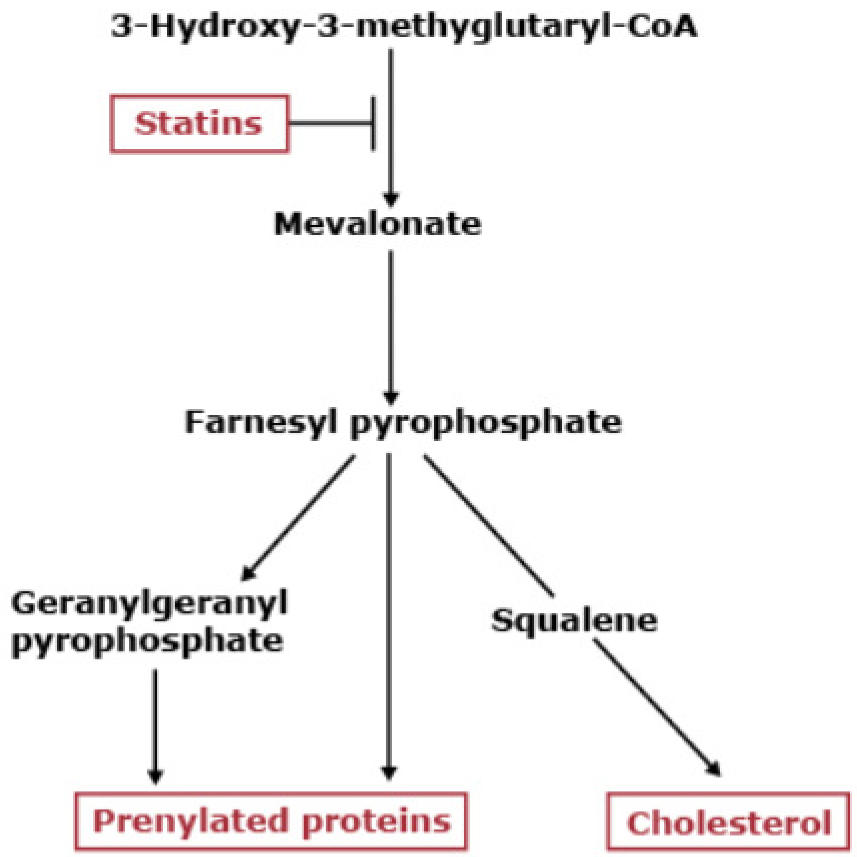
Multiple classes of antihyperlipidemics exist. The statins currently are the most widely used in the United States.

5.2.1 HMG CoA Reductase Inhibitors ("Statins")

The most important drugs for the treatment of dyslipidemias are the HMG CoA reductase inhibitors, or the "statins." Agents in this class include lovastatin (Mevacor), simvastatin (Zocor), atorvastatin (Lipitor), rosuvastatin (Crestor), and pravastatin (Pravachol).

Mechanism of Action The statins are competitive inhibitors of HMG CoA, an enzyme which catalyzes the rate-limiting step in endogenous cholesterol synthesis. When intrinsic cholesterol synthesis is blocked, the liver increases uptake of cholesterol from the plasma through upregulation of hepatic LDL receptors.

Therapeutic Effects Statins have multiple beneficial effects on the plasma lipid profile, including decreases in LDL (30%–60%) and VLDL as well as mild increases in HDL. Statins also exhibit actions beyond lipid-lowering activity, including the improvement of endothelial function, modulation of the inflammatory response, and maintenance of plaque stability.



▲**Figure 3-5.2** Action of HMG CoA Statins

Adverse Effects Statins have an excellent safety record overall, and in controlled trials there is only a small increase in adverse effects compared with placebo. There are some concerns about long-term use and liver damage, but this appears to be quite rare. The more important side effect is myopathy, which ranges from myalgias (~5%-10%), to myositis (~0.5%), to overt rhabdomyolysis (<0.1%). The risk of muscle toxicity increases with higher doses and concurrent therapy with gemfibrozil and nicotinic acid.

Patients should be monitored for abnormalities in liver function tests and symptoms such as muscle aches. Patients who do not tolerate a particular statin may tolerate a different statin.

5.2.2 Fibrates

The three fibrates currently available in the United States include gemfibrozil, fenofibrate, and clofibrate. Clofibrate is infrequently used because of an association with gastrointestinal cancers.

Mechanism of Action Fibrates activate lipoprotein lipase, which promotes catabolism of VLDL.

Therapeutic Effect Fibrates lower serum triglycerides by 35%–50% by reducing VLDL secretion by the liver and increasing clearance of triglycerides through stimulation of lipoprotein lipase. Fibrates also modestly increase HDL cholesterol (~5%).

Adverse Effects Fibrates are generally well tolerated, but have been associated with muscle toxicity. This seems to be more common when given together with statins, and may actually be related to reduced statin metabolism by the fibrate (though fibrate inhibition of CYP3A4).

5.2.3 Bile Acid Sequestrants

Currently available bile acid sequestrants include cholestyramine, colestipol, and colesevelam. As a metabolite of cholesterol, bile acids are one means to eliminate cholesterol from the body.

Mechanism of Action The bile acid sequestrants bind bile acids in the intestine, dramatically decreasing reabsorption of bile acids secreted by the liver. This reduces intrahepatic cholesterol, and secondarily increases LDL receptors, which clear LDL from the plasma.

Therapeutic Effect Bile acid sequestrants modestly reduce LDL (10%–15%) and may minimally increase HDL.

Adverse Effects The major adverse effects of these agents are gastrointestinal, including nausea, bloating, and cramping. These symptoms are related, at least in part, to lipid malabsorption. Bile acid sequestrants impair the absorption of lipophilic drugs (such as digoxin and warfarin) and fat-soluble vitamins (A, D, E, and K).

5.2.4 Nicotinic Acid (Niacin)

Nicotinic acid has actions on plasma lipids unrelated to its mechanism of action as an essential dietary vitamin. For lipid-lowering effects, nicotinic acid is given in much higher doses than are needed as a vitamin. Nicotinic acid is available in immediate-release and sustained-release formulations.

Mechanism of Action Nicotinic acid inhibits the hepatic production of VLDL and consequently its metabolite LDL. Nicotinic acid affects HDL metabolism by reducing the transfer of cholesterol from HDL to VLDL and by delaying hepatic HDL clearance.

Therapeutic Effect Nicotinic acid is very effective for increasing HDL, and may raise levels by as much as 30%–35%. Niacin also causes a decrease in LDL.

Adverse Effects Flushing is the most common side effect and occurs in 80% of patients. Pruritus, paresthesias, and nausea are somewhat less common and occur in about 20% of patients. Symptoms appear to be mediated, at least in part, by the release of prostaglandins from mast cells and can last from 10 minutes up to several hours after dosing.

Side effects tend to be less common with sustained-released formulations, and pretreatment with aspirin 30 minutes before dosing can minimize side effects. Tolerance for niacin improves over time, and compliance improves if patients are started at low doses that are titrated slowly upward.

5.2.5 Cholesterol Uptake Inhibitors

This is a newer lipid-lowering class that includes the agent ezetimibe.

Mechanism of Action Ezetimibe binds to the intestinal lumen and impairs absorption of dietary and biliary cholesterol at the brush border of the intestine.

Therapeutic Effect Ezetimibe can modestly reduce LDL (~15%–20%), and is also effective in combination with a statin. Ezetimibe has not yet been shown to improve clinical outcomes.

Adverse Effects Ezetimibe is very well tolerated, but reported side effects include headache, diarrhea, and rare cases of liver damage. Ezetimibe does not impair the absorption of triglycerides or fat-soluble vitamins.

6 Diuretics

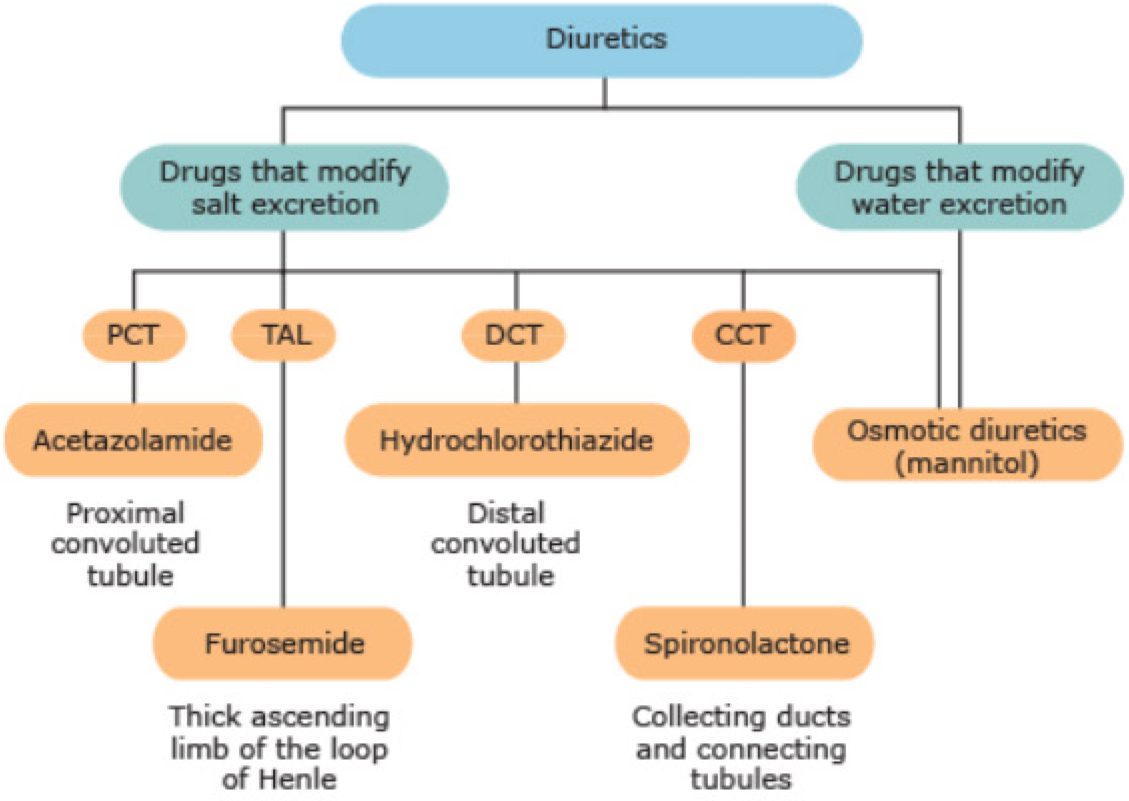
Diuretics are a class of drugs widely used in clinical practice. The various classes of diuretics target different segments of the nephron and thus differentially impact renal reabsorption and clearance of electrolytes.

6.1 Clinical Uses

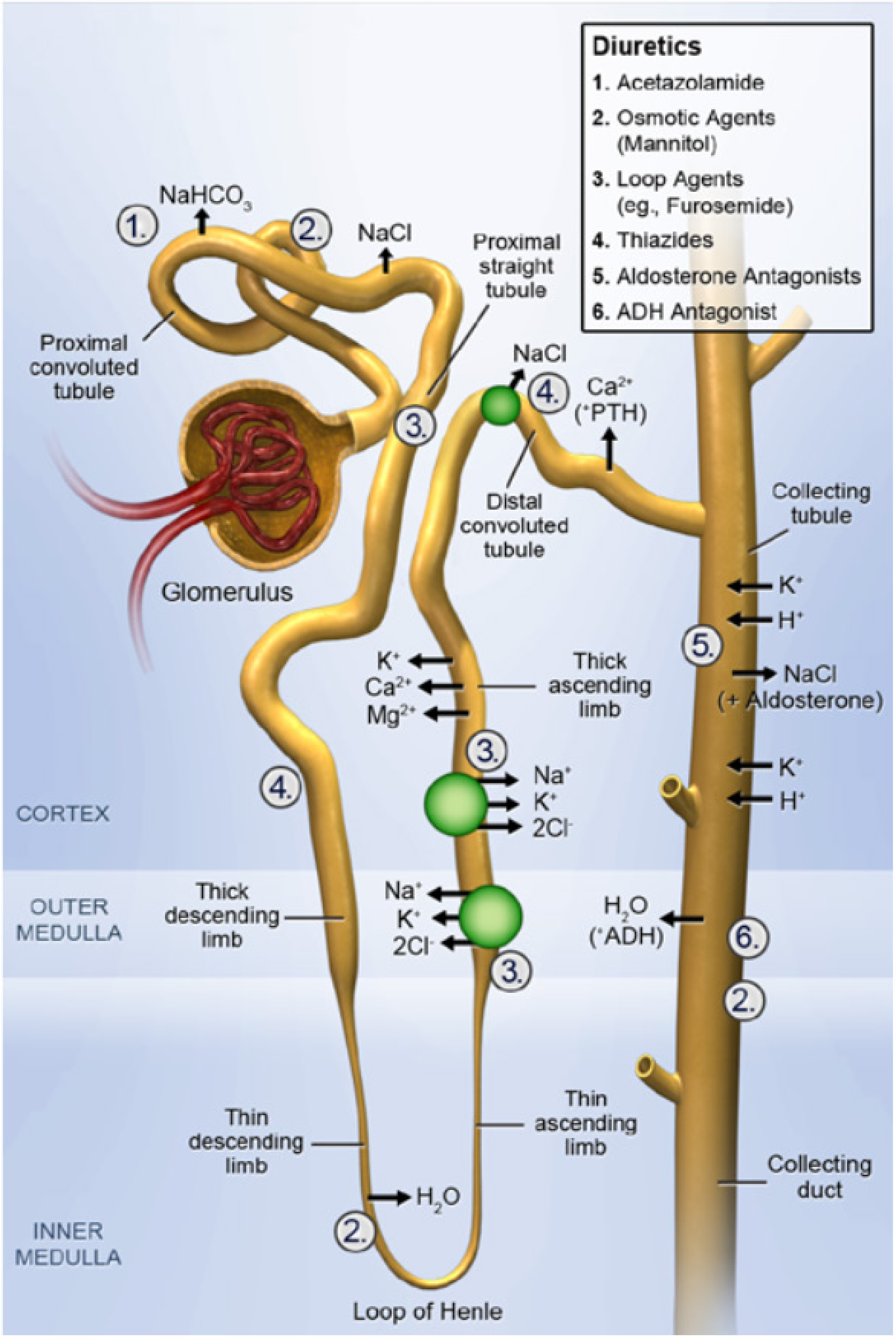
The major clinical uses of diuretics are treatment of *hypertension, congestive heart failure, edema,* and *electrolyte abnormalities*.

6.2 Therapeutic Targets

Most of the diuretics target ion transporters or channels within nephrons. As described below, the site of action influences the efficacy of diuresis.


Diuretics
Drugs that modify salt excretion
Drugs that modify water excretion
PCT
TAL
DCT
CCT
Acetazolamide
Proximal convoluted tubule
Hydrochlorothiazide
Distal convoluted tubule
Osmotic diuretics (mannitol)
Furosemide
Thick ascending limb of the loop of Henle
Spironolactone
Collecting ducts and connecting tubules

▲**Figure 3–6.2A** Diuretic Therapies


Diuretics
1. Acetazolamide
2. Osmotic Agents (Mannitol)
3. Loop Agents (eg., Furosemide)
4. Thiazides
5. Aldosterone Antagonists
6. ADH Antagonist
$NaHCO_3$
1.
2.
NaCl
Proximal straight tubule
Proximal convoluted tubule
3.
NaCl
4.
Ca^{2+} ($^+$PTH)
Glomerulus
Distal convoluted tubule
Collecting tubule
K^+
H^+
5.
NaCl (+ Aldosterone)
K^+
Ca^{2+}
Mg^{2+}
Thick ascending limb
3.
Na^+
K^+
$2Cl^-$
K^+
H^+
4.
CORTEX
OUTER MEDULLA
Thick descending limb
Na^+
K^+
$2Cl^-$
3.
H_2O ($^+$ADH)
6.
2.
Thin descending limb
Thin ascending limb
Collecting duct
H_2O
2.
INNER MEDULLA
Loop of Henle

▲**Figure 3–6.2B** Therapeutic Targets in Renal Transport System

6.3 Major Diuretic Agents

The main diuretics used in clinical settings fall into the following classes:

- Osmotic diuretics
- Carbonic anhydrase inhibitors
- Loop diuretics
- Thiazides
- Potassium-sparing diuretics

6.3.1 Osmotic Diuretics

The osmotic diuretics include mannitol, glycerin, and isosorbide, with mannitol being the most commonly used agent in this class. This class of diuretics is used infrequently compared to the thiazides and loop diuretics.

Mechanism of Action The osmotic diuretics are relatively inert pharmacologically, are freely filtered at the glomerulus, and undergo little or no reabsorption by the renal tubule. The main effect of these agents is to increase *water* (rather than Na^+) excretion. The osmotic diuretics pull water out of the tissues into the blood, enhancing the excretion of H_2O.

Therapeutic Uses The main uses of osmotic diuretics are to reduce intracranial pressure in *cerebral edema,* reduce intraocular pressure during acute attack of *glaucoma,* and preserve urine volume in acute *renal failure*. Osmotic diuretics are rarely used for any extended period of time.

Adverse Effects Changes in intracranial pressure caused by osmotic diuretics can lead to dizziness, nausea, and vomiting. Also, the increase in extracellular fluid volume can lead to pulmonary edema in patients with congestive heart failure and/or marginal renal status.

6.3.2 Carbonic Anhydrase Inhibitors

The carbonic anhydrase inhibitors are currently represented by acetazolamide and dorzolamide. These drugs are rarely used clinically for diuresis but does have some niche clinical applications.

Mechanism of Action Acetazolamide inhibits carbonic anhydrase in the proximal tubular epithelial cells. This leads to excretion of sodium bicarbonate and development of a *metabolic acidosis* during chronic use. Acetazolamide is a weak diuretic because most of the reabsorption of sodium occurs distal to the site of action of acetazolamide.

Therapeutic Uses Acetazolamide has few clinical applications. The drug is used to *prevent mountain sickness* by offsetting the respiratory alkalosis common at high altitudes (due to rapid breathing) with a metabolic acidosis. Acetazolamide is also used to treat simple *(open angle) glaucoma* by decreasing formation of aqueous humor. Lastly, acetazolamide is used to treat elevated intracranial pressure due to buildup absorption of CSF.

Adverse Effects Acetazolamide's most common adverse effect is metabolic acidosis—which, in some cases, is a desired result for preventing mountain sickness. Allergic reactions are also seen, as this is a sulfonamide-like drug.

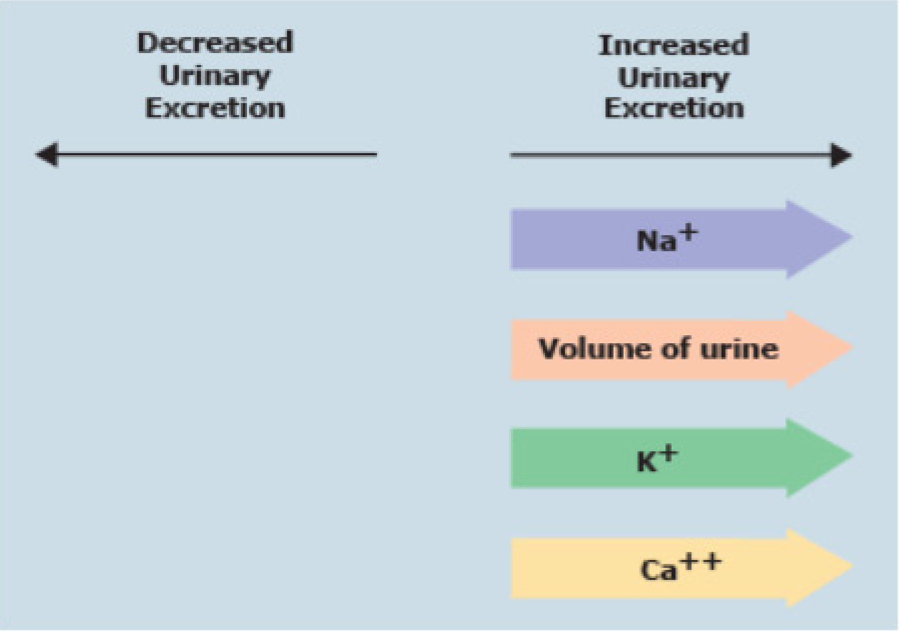
6.3.3 Loop Diuretics

Loop diuretics are widely used for treatment of edema, hypertension, and renal insufficiency. The most commonly used loop diuretics are:

- Furosemide (most widely used, short half-life of ~90 minutes)
- Bumetanide
- Ethacrynic acid (not a sulfur compound, no sulfa allergies; intravenous)
- Torsemide

Mechanism of Action Loop diuretics inhibit the Na^+-K^+-$2Cl^-$ cotransporter in the thick ascending loop of Henle. Loop diuretics are powerful diuretics in that they block a major site of electrolyte reabsorption. Loop diuretics lead to increased excretion of Na^+, K^+, Cl^-, Ca^{2+}, and Mg^{2+}.

Therapeutic Uses Loop diuretics are most widely used for treatment of *pulmonary edema,* congestive heart failure (especially decompensated heart failure exacerbation), and acute renal failure. Less common uses are treatment of *hypertension* and *hypercalcemic states*. Torsemide is often used to treat edema associated with cirrhosis.



▲**Figure 3–6.3A** Loop Diuretics

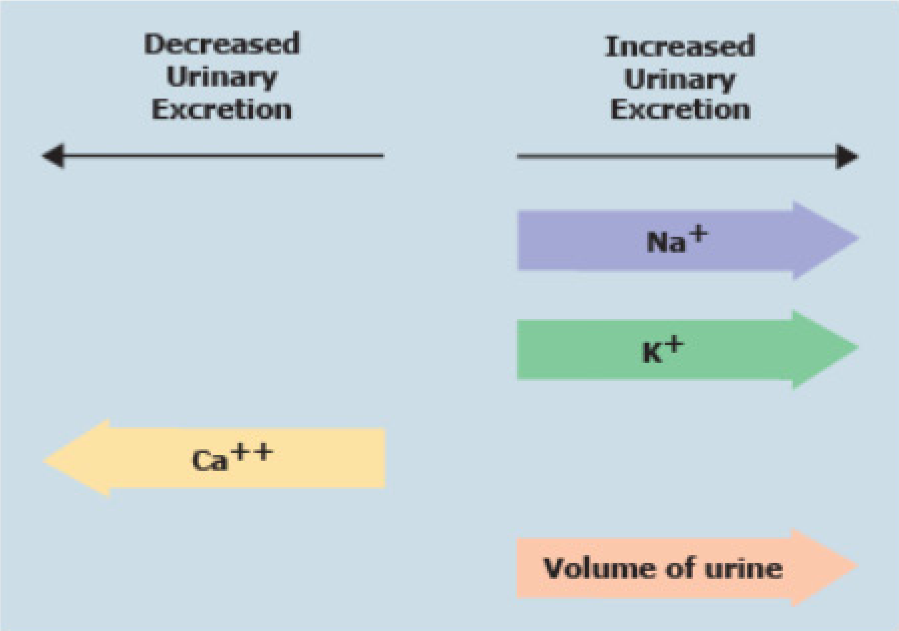
Adverse Effects The powerful effects of loop diuretics leave them prone to inducing *electrolyte abnormalities*. Hypokalemia is a common problem and presents a special danger if loop diuretics are used together with digoxin, whose toxicity is enhanced by *low potassium*. The loop diuretics can also cause ototoxicity and nephrotoxicity. Hyponatremia, volume depletion, and contraction alkalosis can also be seen. Less common side effects are hyperuricemia and allergic reactions. Intravenous ethacrynic acid is rarely associated with ototoxicity.

6.3.4 Thiazides

The thiazides are the most commonly prescribed of the diuretics. They are used mainly in the chronic management of hypertension. The thiazides used clinically are:

- Hydrochlorothiazide (most commonly used; first-line for hypertension)
- Chlorthalidone
- Metolazone (usually used only for congestive heart failure)
- Indapamide

Mechanism of Action Thiazides inhibit the Na+/Cl- cotransporter in the distal convoluted tubule. They are less efficacious than loop diuretics since 90 percent of the Na+ filtered through the glomerulus is already reabsorbed prior to the distal convoluted tubule. Thiazide diuretics lead to increased excretion of Na+, K+, and Cl-, but *decreased excretion of Ca2+*.



▲**Figure 3–6.3B** Thiazides

Therapeutic Uses Thiazides are commonly used to treat hypertension, congestive heart failure, nephrolithiasis, and edematous states. Thiazides are not as effective as loop diuretics in patients with poor renal function.

Adverse Effects Like loop diuretics, thiazides can lead to *hypokalemia,* hyponatremia, volume depletion, and contraction alkalosis. Unlike loop diuretics, thiazides can cause hypercalcemia. Other common side effects are headache and impotence. Less common adverse effects are hyperglycemia (possibly due to impaired insulin release) and hyperlipidemia (mechanism unknown).

6.3.5 Potassium-Sparing Diuretics

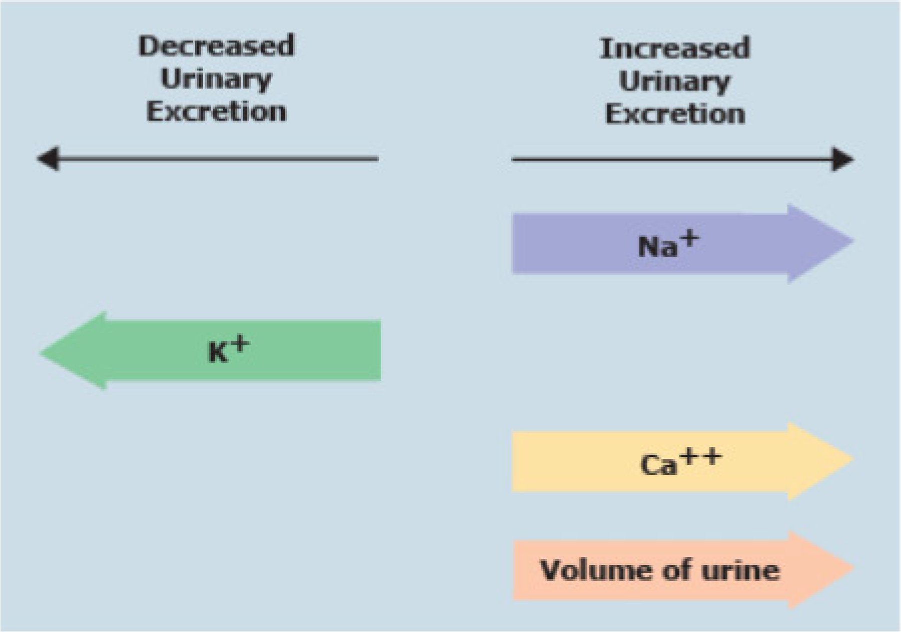
The potassium-sparing diuretics are actually a collection of drugs with two main mechanisms: inhibition of aldosterone receptors (spironolactone and eplerenone) or inhibition of sodium channels (amiloride and triamterene).

Mechanism of Action Amiloride and triamterene inhibit sodium channels in late distal convoluted tubule and collecting ducts. Spironolactone is an aldostesone antagonist and promotes water and sodium excretion. Eplerenone is a weak diuretic with fewer antiandrogenic effects than spironolactone.

Therapeutic Uses The potassium-sparing diuretics are rarely employed as single agents and instead are often used to offset the potassium wasting effects of loop or thiazide diuretics. Because they act very distally in the nephron, potassium-sparing diuretics are weak in terms of diuretic effect. Other uses more specific to the individual agents are discussed below.

- Triamterene is sometimes used for management of mild hypertension.
- Amiloride is classically used in the management of lithium-induced diabetes insipidus.
- *Spironolactone* has recently become popular for its anti-hypertensive properties, especially in patients with congestive heart failure by preventing pathologic *cardiac "remodeling."* This agent is not totally selective for the mineralocorticoid receptor and also inhibits androgen and progesterone receptors. This can be used to clinical advantage in the treatment of *polycystic ovary disease.*
- During the EPHESUS trial, eplerenone (Inspra) demonstrated benefit for eplerenone in post-myocardial infarction patients with left ventricular dysfunction.

Adverse Effects Spironolactone can lead to unwanted side effects such as *gynecomastia,* impotence, *hirsutism,* and menstrual irregularities. Amiloride is generally well-tolerated. Triamterene can rarely cause renal stones. All of the potassium-sparing diuretics have the potential to cause *hyperkalemia,* especially when used on their own.



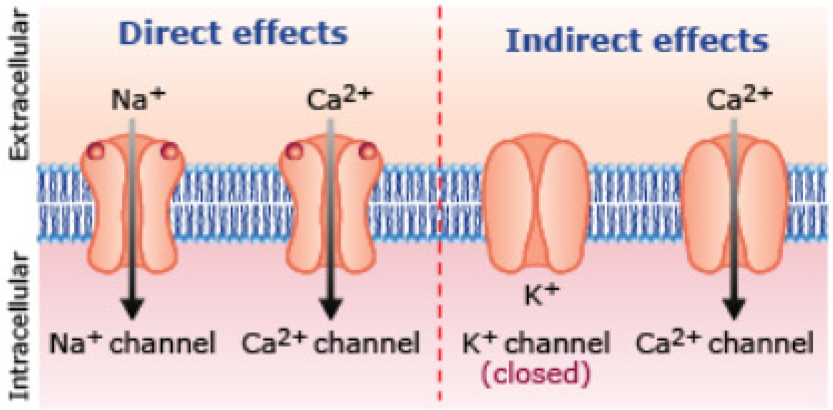
▲ **Figure 3–6.3C** Potassium-Sparing Diuretics

CHAPTER 4 Neuropharmacology

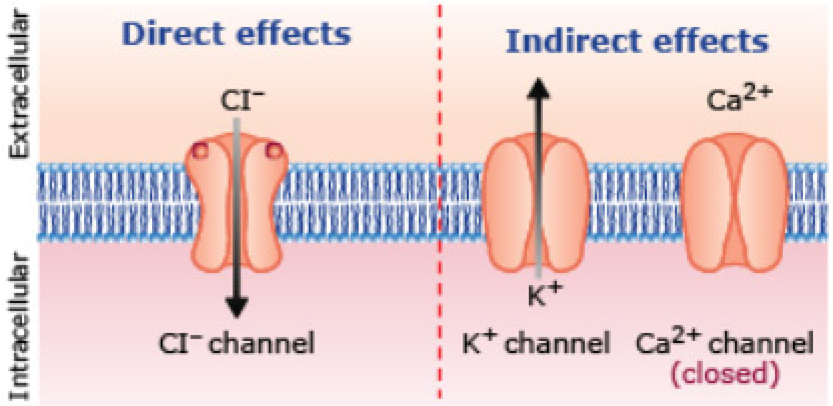
1 Neurotransmitters and Their Receptors

Many important neurotransmitters exist in the central nervous system (CNS). Different neurotransmitters can either excite or inhibit other neurons from firing. Excitatory neurotransmitters activate receptors that allow sodium and calcium to enter the neuron and depolarize the cell, thereby increasing probability for action potentials. Inhibitory neurotransmitters tend to activate receptors that allow negatively charged chloride to enter the cell or positively charged potassium to exit the cell, thereby hyperpolarizing the cell and decreasing the probability of action potentials.

Effects of Excitatory Neurotransmitters


Extracellular
Intracellular
Direct effects
Indirect effects
Na^+
Ca^{2+}
Ca^{2+}
K^+
Na^+ channel
Ca^{2+} channel
K^+ channel
(closed)
Ca^{2+} channel

Effects of Inhibitory Neurotransmitters


Extracellular
Intracellular
Direct effects
Indirect effects
Cl^-
Ca^{2+}
K^+
Cl^- channel
K^+ channel
Ca^{2+} channel
(closed)

▲**Figure 4-1.0** Excitatory vs. Inhibitory Neurotransmitters

1.1 Glutamate

Glutamate is considered to be the primary excitatory neurotransmitter in the CNS. Some glutamate receptors are ion channels themselves (ionotropic) and others are coupled to second messenger systems (metabotropic). There are very few clinically used drugs that target the glutamate receptors. Some important glutamate receptor subtypes are the NMDA, kainate, and AMPA receptors. Phencyclidine and ketamine are antagonists of the NMDA glutamate receptor.

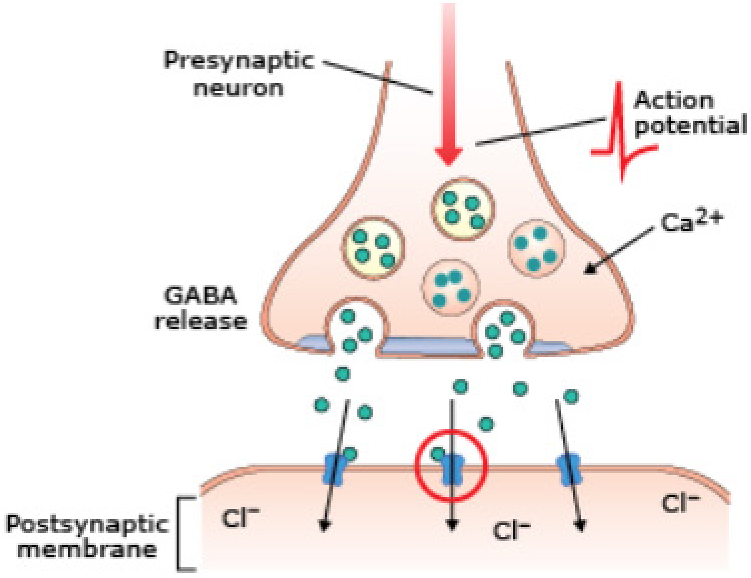
USMLE™ Key Concepts

For Step 1, you must be able to:

- Identify the major neurotransmitter receptors in the central nervous system and the clinically used drugs that activate or inhibit these receptors.
- Describe the mechanism of action, therapeutic uses, and adverse effects of sedative-hypnotics, general anesthetics, local anesthetics, neuromuscular blockers, opioids, antidepressants, antipsychotics, mood stabilizers, and anti-Parkinson drugs.
- Explain the mechanism of action and adverse effects associated with cannabis and central nervous system stimulants.

1.2 GABA

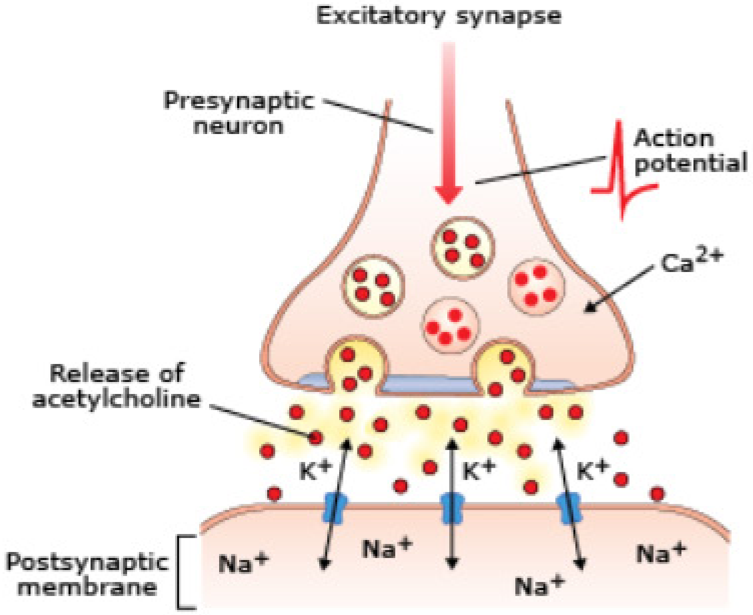
GABA (γ-aminobutyric acid) receptors are divided into two major categories, both of which are inhibitory. The GABA_A receptors are ionotropic receptors and GABA_B receptors are metabotropic-G-protein-coupled receptors (GPCRs). GABA_A receptors are the targets of many sedative-hypnotics, such as benzodiazepines, and general anesthetics, such as propofol. GABA_B receptors are the targets of some muscle relaxants, such as baclofen.


Presynaptic neuron
Action potential
Ca^{2+}
GABA release
Postsynaptic membrane
Cl^-
Cl^-
Cl^-

▲ **Figure 4-1.2** GABAergic Terminal

1.3 Acetylcholine

There are two main types of acetylcholine (ACh) receptor: muscarinic and nicotinic. Nicotinic ACh receptors are involved in skeletal muscle contraction. Antibodies against the muscle nicotinic acetylcholine receptor cause the disease myasthenia gravis. Botulinum toxin inhibits the release of acetylcholine from the presynaptic vesicles in a neuron and thereby causes paralysis. Botulinum toxin (Botox) is used for a variety of applications including the treatment of strabismus, blepharospasm, cervical dystonia, and excessive sweating, in addition to cosmetic surgery (to remove skin wrinkles).


Excitatory synapse
Presynaptic neuron
Action potential
Ca^{2+}
Release of acetylcholine
K^+
K^+
K^+
Postsynaptic membrane
Na^+
Na^+
Na^+
Na^+

▲ **Figure 4-1.3** Cholinergic Synapse

1.4 Dopamine

Dopamine is another important CNS neurotransmitter. CNS stimulants, such as amphetamine and cocaine, are able to increase dopaminergic activity by blocking the transporter that reuptakes dopamine from the synaptic cleft. Dopamine activity is decreased in Parkinson disease, where there is a loss of dopaminergic substantia nigra neurons. Most antipsychotic medications are antagonists at dopamine receptors.

1.5 Norepinephrine

Norepinephrine receptors have multiple subtypes that are found in several areas of the brain. The receptors are especially found in the locus coeruleus, which is important for stress, panic, attention, alertness, and the sleep-wake cycle.

1.6 Serotonin

Serotonin, also known as 5-hydroxytryptamine (5-HT), is a monoamine important to both the central and peripheral nervous systems. There are seven different families of serotonin receptors, all of which are metabotropic GPCRs except the 5-HT_3 receptor, which is a ligand-gated ion channel. The most important drug types targeting the serotonin system are the antidepressants, especially the selective serotonin reuptake inhibitors, as well as some antiemetic drugs and migraine medications.

1.7 Opioids

Opioid receptors are metabotropic inhibitory receptors coupled to second messenger systems. These have a role in the modulation of pain, and they are the target of opioid medications such as morphine and hydrocodone. The human body also creates endogenous opioids, such as endorphin and enkephalin, that activate these receptors.

1.8 Cannabinoids

Cannabinoid receptors are GPCRs found in the CNS and on immune cells. Cannabinoid receptor 1 (CB1) is mainly located in the basal ganglia, limbic system, and brainstem areas important for respiratory and cardiovascular control. Activation of CB1 will cause relaxation, fatigue, analgesia, alteration of the senses, and increased appetite. CB2 is mainly located on immune cells. The functions of the endogenous cannabinoids are poorly understood.

1.8.1 Cannabis (Marijuana)

Marijuana is a Schedule 1 controlled substance, although some states allow limited use for medicinal purposes. The active component in marijuana is delta Δ^9-tetrahydrocannabinol (THC), which produces its effects through activation of CB1 receptors. Marijuana contains about 1% to 10% THC by weight. Other formulations, such as hashish, contain more THC.

1.8.2 Therapeutic Use and Adverse Effects

Marijuana has many psychological effects. It causes euphoria and relaxation as well as analgesia in some patients. It also can prevent nausea and vomiting, and it is able to decrease intraocular pressure. Marijuana use is not known to cause prominent tolerance or physical or psychological dependence. Chronic use leads to CNS changes, such as lethargy.

2 Sedative-Hypnotic Drugs

Sedative-hypnotic drugs depress the CNS, resulting in sedation (decreased motor activity), hypnosis (sleep), and decreased anxiety. Drugs within this class are used to treat a variety of clinical applications including anxiety and insomnia, as well as to provide sedation prior to surgery or an invasive procedure. The trend over the last several decades has been away from the use of drugs with a high risk of respiratory depression, such as barbiturates and chloral hydrate, to the use of benzodiazepines and benzodiazepine-like hypnotics.

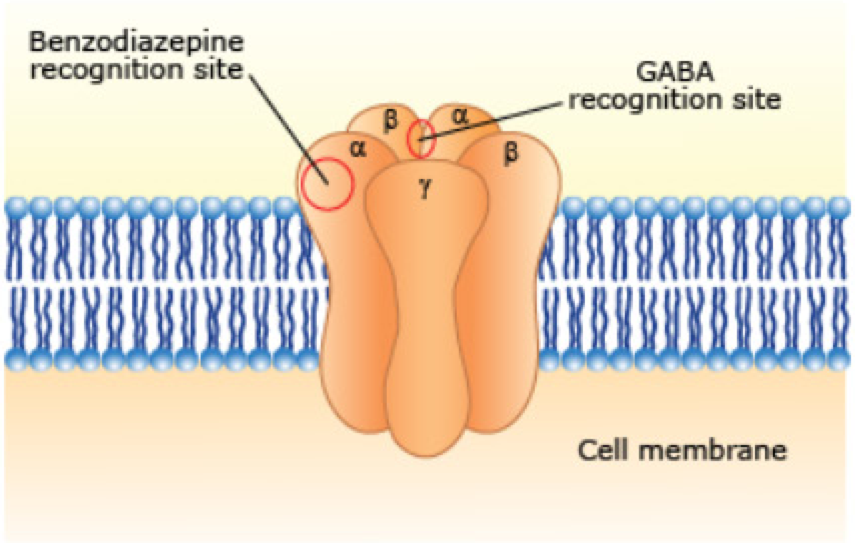
2.1 Benzodiazepines

The benzodiazepines currently are the most frequently prescribed class of sedative-hypnotics. This class of drugs is extremely versatile. Several are consistently in the top 50 most-prescribed medications in the United States. The therapeutic applications of benzodiazepines are diverse:

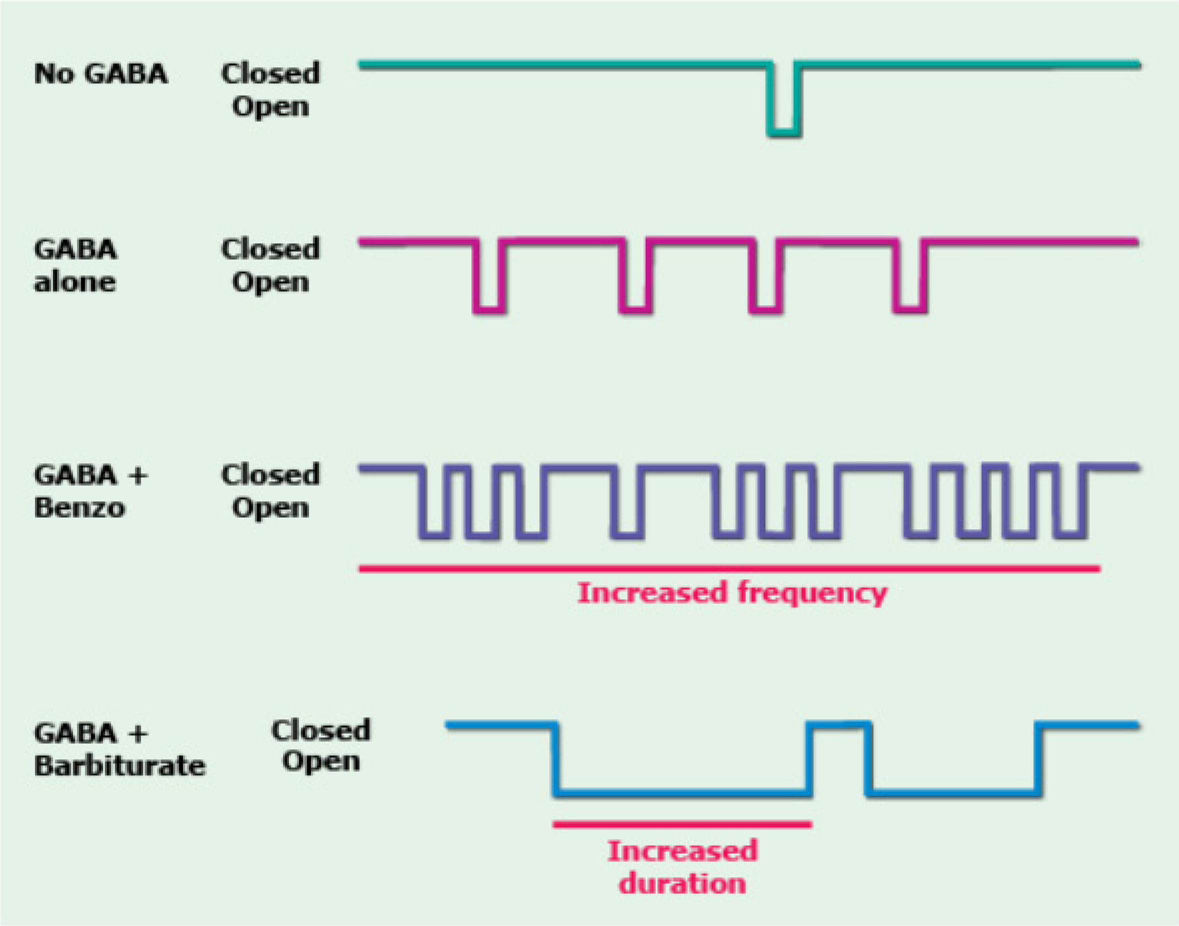
- Short-term treatment of anxiety disorders
- Insomnia
- Seizures
- Pre-anesthesia
- Muscle relaxation
- Management of drug withdrawal states (e.g., delirium tremens for ethanol)
- Agitation in acute mania

2.1.1 Mechanism of Action

The benzodiazepines bind to the GABA$_A$ receptor at a site distinct from the GABA agonist site and enhance the actions of GABA. This mechanism is referred to as positive allosteric modulation. Benzodiazepines increase the frequency of chloride ion channel openings produced by GABA. This leads to overall increased chloride influx that hyperpolarizes the cells and inhibits the generation of action potentials.



▲**Figure 4-2.1A** GABA$_A$ Receptor Structure



▲**Figure 4-2.1B** Action of Benzodiazepines and Barbiturates on GABAA Receptor

2.1.2 Pharmacokinetics

The duration of action of benzodiazepines is influenced by their metabolism. Some benzodiazepines are short-acting (minutes) while others are long-acting (hours to days). Diazepam has multiple active metabolites that contribute to its long therapeutic duration of action. Benzodiazepines are often classified by their duration.

2.1.3 Adverse Effects

The benzodiazepines are much safer than the older generation of barbiturate sedative-hypnotics, especially when used in overdose. Fatal benzodiazepine ingestions are rare, although fatalities can occur when benzodiazepines are combined with other CNS depressants such as alcohol or γ-hydroxybutyrate (GHB). Benzodiazepines have relatively low abuse liability (hence classification of many as Schedule IV controlled substances); however, physical and psychological dependence can occur with chronic use. Other common side effects include:

- Daytime drowsiness and sedation (particularly with long-acting agents)
- Rebound insomnia (especially with short-acting agents)

Flumazenil is a specific antidote for benzodiazepines that prevents benzodiazepines but not GABA from binding to the $GABA_A$ receptor.

2.1.4 Alprazolam

Alprazolam (Xanax) is an intermediate-duration (5 to 24 hours) benzodiazepine widely used for the treatment of anxiety, panic disorder, and phobias.

2.1.5 Diazepam

Diazepam (Valium) is a long-acting (> 24 hours) benzodiazepine that is used for the treatment of anxiety disorders, seizures, delirium tremens, and muscle spasms. The long duration of diazepam is caused in part by several active metabolites. Diazepam is typically not an appropriate drug for the treatment of insomnia because of the long duration of action.

2.1.6 Clonazepam

Clonazepam (Klonopin) is an intermediate-duration benzodiazepine used for the management of anxiety disorders. It is also used to treat seizures.

2.1.7 Lorazepam

Lorazepam (Ativan) is an intermediate-duration benzodiazepine used for the treatment of anxiety, seizures, and muscle spasms. Lorazepam is probably the most widely used benzodiazepine for providing sedation in newborns and infants.

2.1.8 Midazolam

Midazolam (Versed) is a short-acting benzodiazepine commonly used as a "preanesthetic" to provide sedation prior to surgery or invasive procedure such as colonoscopy. The combination of midazolam with the opioid fentanyl is very common for providing sedation during colonoscopy and bronchoscopy procedures.

2.1.9 Flunitrazepam

Flunitrazepam (Rohypnol) is a short-acting benzodiazepine that was never approved for medical use in the United States. Flunitrazepam is used as a "date rape" drug in that it can rapidly depress consciousness in an unsuspecting victim.

2.1.10 Other Benzodiazepines

Other benzodiazepines used are listed in the accompanying table. Of note, triazolam (Halcion) was once widely used for insomnia but has been supplanted by the non-benzodiazepines (e.g., zolpidem). Temazepam is prescribed for insomnia.

▼Table 4-2.1 Benzodiazepines

(Half-Life)	Primary Indicators
Short acting ($t_{1/2}$ < 5 h)	
Midazolam	Preanesthetic
Triazolam	Insomnia, preanesthetic
Intermediate acting ($t_{1/2}$ 5–24 h)	
Alprazolam	Anxiety, antidepressant
Clonazepam	Seizures
Estazolam	Insomnia
Lorazepam	Anxiety, insomnia, seizures, preanesthetic
Oxazepam	Anxiety
Temazepam	Insomnia
Long-lasting ($t_{1/2}$ < 24 h)	
Chlordiazepoxide	Anxiety, preanesthetic, withdrawal states
Clorazepate	Anxiety, seizures
Diazepam	Anxiety, preanesthetic, seizures, withdrawal states
Flurazepam	Insomnia
Prazepam	Anxiety
Quazepam	Insomnia

2.2 Barbiturates

The barbiturates were once the dominant sedative-hypnotics but have been supplanted by safer drugs such as the benzodiazepines and zolpidem for treatment of anxiety, insomnia, and agitation. The clinical applications of barbiturates have now narrowed to a small list:

- Anticonvulsants (phenobarbital, primidone)
- Anesthetic induction (thiopental)
- Drug-induced coma for severe brain trauma (pentobarbital)
- Component of lethal injection in some states for capital punishment

Other barbiturates used in previous decades (e.g., amobarbital, secobarbital) are virtually never encountered even as drugs of abuse.

2.2.1 Mechanism of Action

The barbiturates have a similar mechanism of action to benzodiazepines, with the exception that barbiturates increase the duration (and not frequency) of chloride ion channel opening of the $GABA_A$ receptor. The barbiturates have higher efficacy than benzodiazepines in allosterically modulating the actions of GABA.

2.2.2 Pharmacokinetics

Phenobarbital is a strong inducer of cytochrome P450 (CYP) enzymes, which can lead to drug-drug interactions involving CYP substrates. An example would be increased degradation of cyclosporine.

2.2.3 Adverse Effects

The major adverse effect with barbiturates is powerful CNS and respiratory depression. Overdose, especially when combined with another CNS depressant such as ethanol, can easily lead to coma and death. Barbiturate-related deaths, from both intentional and unintentional overdoses, were a common cause of death in the 1960s and 1970s. Unlike benzodiazepines, barbiturates have no antidote. Chronic abuse of barbiturates can lead to tolerance and dependence. Sudden withdrawal from barbiturate therapy can lead to anxiety, agitation, hyperreflexia, and seizures.

2.3 Chloral Hydrate

Chloral hydrate is an older alcohol sedative-hypnotic. It has very limited clinical use, mostly confined to providing sedation in children prior to imaging procedures that require the child to remain still. It is not an acceptable option to treat insomnia, given that it is dangerous in overdose and has no specific antidote.

Important Concept

Overdose of barbiturates and chloral hydrate is much more dangerous than overdose of benzodiazepine and benzodiazepine-like drugs.

2.4 Benzodiazepine-Like Sedative-Hypnotics

Zolpidem (Ambien), zaleplon (Sonata), and eszopiclone (Lunesta) are benzodiazepine-like drugs that likely have similar mechanism to benzodiazepines in allosterically enhancing the effect of GABA at $GABA_A$ receptors. These drugs have become the medications of choice for the short-term management of insomnia. Typically, it is not recommended that these be taken for extended periods. All three drugs are much safer in overdose compared to benzodiazepines and especially barbiturates, and also have lower abuse liability. Deaths due to overdose of zolpidem, zaleplon, or eszopiclone are rare.

Important Concept

Zolpidem, zaleplon, and eszopiclone are the drugs of choice for the short-term management of insomnia.

2.5 Ramelteon

Ramelteon is an agonist at melatonin receptors MT1 and MT2 in suprachiasmatic nucleus of the hypothalamus. Ramelteon is FDA-approved for insomnia, particularly in patients with issues with delayed sleep onset. In contrast to benzodiazepines, ramelteon has not shown issues with dependence. The major adverse effect is hyperprolactinemia.

2.6 Herbal Sedative-Hypnotics

Two herbal products, kava and valerian, are used as sleep aids and anxiolytics.

2.6.1 Kava

Kava, also known as kava-kava, is an herbal product used as a sleep aid and anxiolytic. Kava use is associated with liver damage.

2.6.2 Valerian

Valerian is an herbal product used as a sleep aid and anxiolytic. Active compounds in valerian act as allosteric modulators at $GABA_A$ receptors (similar to benzodiazepines).

2.7 γ-Hydroxybutyrate

γ-Hydroxybutyrate (GHB) is a naturally occurring neurotransmitter that also is used as a drug. GHB has FDA approval for the management of narcolepsy, especially cataplexy (loss of muscle tone).

GHB also has notoriety as a "date rape" drug. GHB, which can be slipped into drinks, produces rapid unconsciousness. GHB is not detected by typical drug screens.

Important Concept

Flunitrazepam and GHB are the two most widely abused date rape drugs. Both are tasteless and colorless, can be slipped into drinks surreptitiously, rapidly depress consciousness, and produce short-term amnesia effects.

3 Antiepileptic Drugs

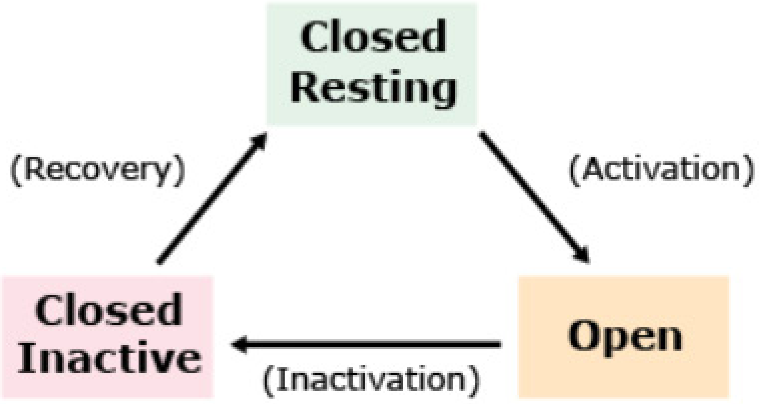
Patients who have seizure disorders experience episodic discharges of electricity in the brain that are associated with either excessive or hypersynchronous depolarization of neurons. Epilepsy is characterized by recurrent seizures that are due either to an inherited or acquired brain disorder. Seizures can present in various ways. Some patients have generalized seizures that involve the whole brain, such as grand mal seizures, and others have partial seizures that involve only a part of the brain, such as simple partial seizure. Pharmacotherapy is often started in patients who have had two or more unprovoked seizures.

3.1 Phenytoin

Phenytoin (Dilantin) is an older but frequently used anticonvulsant. Phenytoin is used for management of partial seizures as well as tonic-clonic seizures.

3.1.1 Mechanism of Action

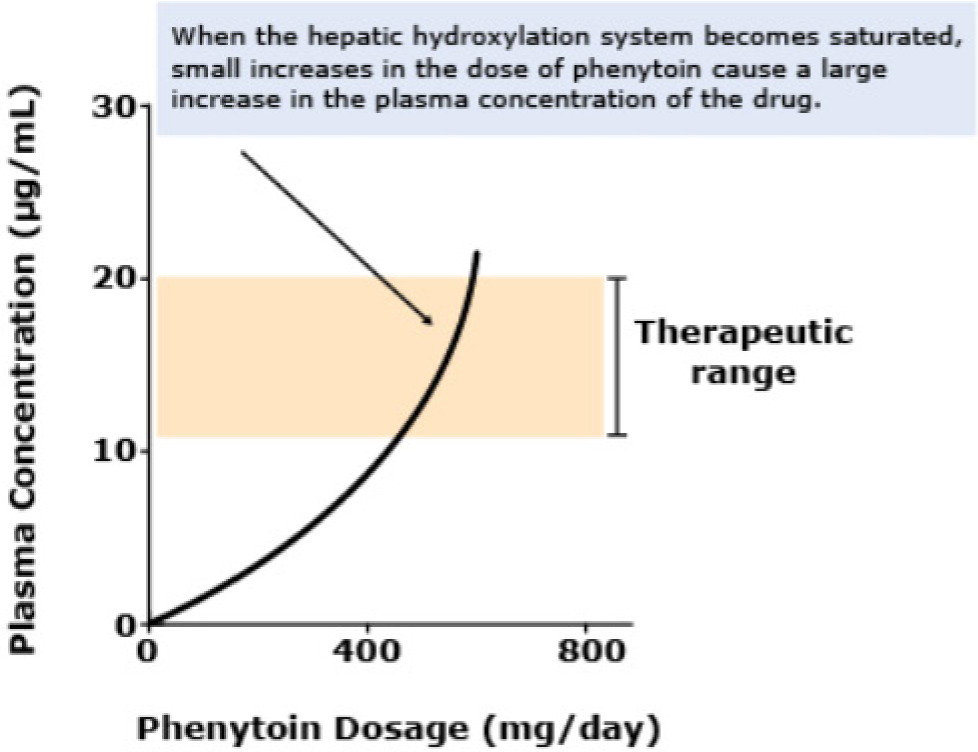
Phenytoin blocks voltage-gated sodium channels by keeping them in an inactivated state. The inactivated state of the sodium channel is distinct from the normal open and closed states. Phenytoin does not completely block sodium channel opening and closing but does limit high-frequency activity.



▲**Figure 4-3.1A** Different States of Sodium Ion Channel

3.1.2 Pharmacokinetics

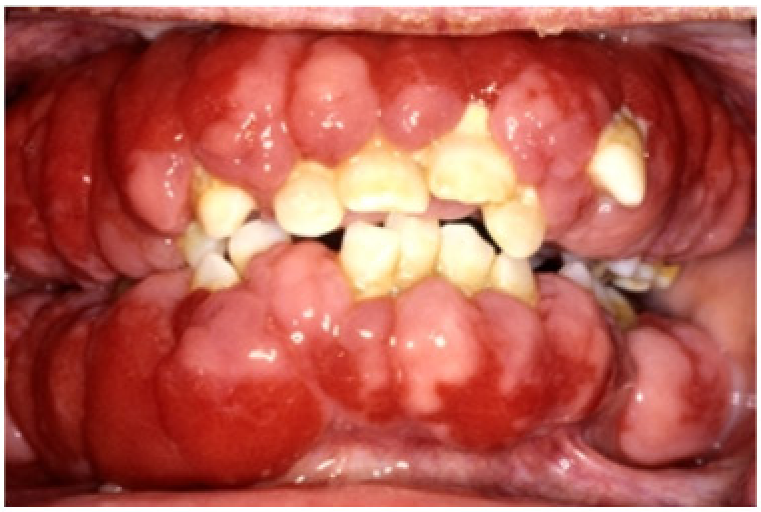
Phenytoin is a very difficult drug to dose because of its complex pharmacokinetics. Phenytoin shows zero-order elimination kinetics, meaning that as the concentration increases the elimination does not increase proportionally due to saturation of the enzymes that metabolize phenytoin. It also has a great deal of first-pass metabolism in the liver, and it induces multiple cytochrome P450 enzymes, which can cause drug-drug interactions such as increased degradation of estrogen-containing oral contraceptives.



▲**Figure 4-3.1B** Zero-Order Elimination Kinetics of Phenytoin

3.1.3 Adverse Effects

Common effects of phenytoin include sedation (very common), ataxia, diplopia, and gingival overgrowth. Phenytoin can also cause osteomalacia (due to enhanced metabolism of vitamin D) and Stevens-Johnson syndrome more commonly than other medications. It also can cause a block of insulin release from islet cells, causing diabetes. Phenytoin can be given intravenously; however, the high alkalinity of the intravenous solution can cause pain on injection. Phenytoin should never be used during pregnancy because of its teratogenic effects.



Edward H. Gill/Custom Medical Stock Photo

▲**Figure 4-3.1C** Teeth and Gums After Long-Term Phenytoin Therapy

3.2 Fosphenytoin

Fosphenytoin is a water-soluble prodrug of phenytoin. The main advantage of fosphenytoin is that it can be rapidly infused without the adverse effects associated with the highly alkaline phenytoin intravenous solution. Fosphenytoin is one of the drugs of choice for emergency treatment of status epilepticus.

Looking Back

Phenytoin use in pregnancy, especially the first trimester, is associated with the *fetal hydantoin syndrome,* which can present with a wide range of anomalies, including intrauterine growth retardation, microcephaly, craniofacial abnormalities, hypoplastic fingernails or toes, developmental delay, and mental retardation.

3.3 Carbamazepine

Carbamazepine (Tegretol) has similar therapeutic uses to phenytoin in treating epilepsy. It is the drug of choice for trigeminal neuralgia and is also used to treat bipolar disorder.

3.3.1 Mechanism of Action

Carbamazepine has a similar mechanism of action to phenytoin. It also has anticholinergic, antineuralgic, antidiuretic, muscle relaxant, antimanic, antidepressive, and antiarrhythmic properties.

3.3.2 Pharmacokinetics

The pharmacokinetics of carbamazepine are similar to those of phenytoin.

3.3.3 Adverse Effects

The side effects of carbamazepine are the same as phenytoin except that it does not cause gingival hyperplasia.

3.4 Ethosuximide

Ethosuximide (Zarontin) is another anti-seizure medication that works by blocking calcium ion currents in the thalamus and motor cortex. Consequently, the threshold for seizure activation increases. It is the drug of choice for treating absence seizures.

3.5 Valproic Acid

Valproic acid is used for general or partial seizures, as well as treatment of bipolar disorder and migraine headaches. Valproic acid is known to cause hepatotoxicity; therefore, patients need liver function to be tested periodically. It is not recommended for pregnant women because of an increased risk of neural tube defects.

3.6 Lamotrigine

Lamotrigine (Lamictal) is another anti-seizure medication that works by inhibiting voltage-gated sodium channels. It frequently is used as adjuvant therapy for a variety of seizure disorders such as generalized tonic-clonic, absence seizures, and partial seizures. It also is used to treat bipolar disorder. Lamotrigine has one of the highest rates of dermatologic reactions, including Stevens-Johnson syndrome, but it does have a very good safety record in pregnancy. Lamotrigine doses are titrated slowly. The drug is discontinued if any dermatologic reaction occurs.

3.7 Gabapentin

Gabapentin has an unclear mechanism of action. Although originally used for epilepsy, gabapentin is now much more commonly used for management of chronic pain. A related drug, pregabalin (Lyrica), also is commonly used for chronic pain.

3.8 Topiramate

Topiramate (Topamax) is an anti-seizure medicine that blocks voltage-gated sodium channels. It also is a weak inhibitor of carbonic anhydrase, so it has a minor diuretic effect.

3.9 Vigabatrin

Vigabatrin (Sabril) is a newer anticonvulsant. It is an inhibitor of the enzyme that degrades GABA (GABA-transaminase), which consequently increases the amount of GABA. It is known to cause visual field defects as a side effect.

3.10 Drugs for Tonic-Clonic Seizures

The drugs typically used for tonic-clonic seizures are:

- Phenytoin
- Carbamazepine
- Phenobarbital (or the related drug primidone)
- Valproic acid

3.11 Drugs for Absence Seizures

The drugs commonly used for absence seizures are:

- Ethosuximide
- Valproic acid
- Clonazepam
- Lamotrigine

3.12 Drugs for Status Epilepticus

The drugs of choice for status epilepticus (medical emergency) are:

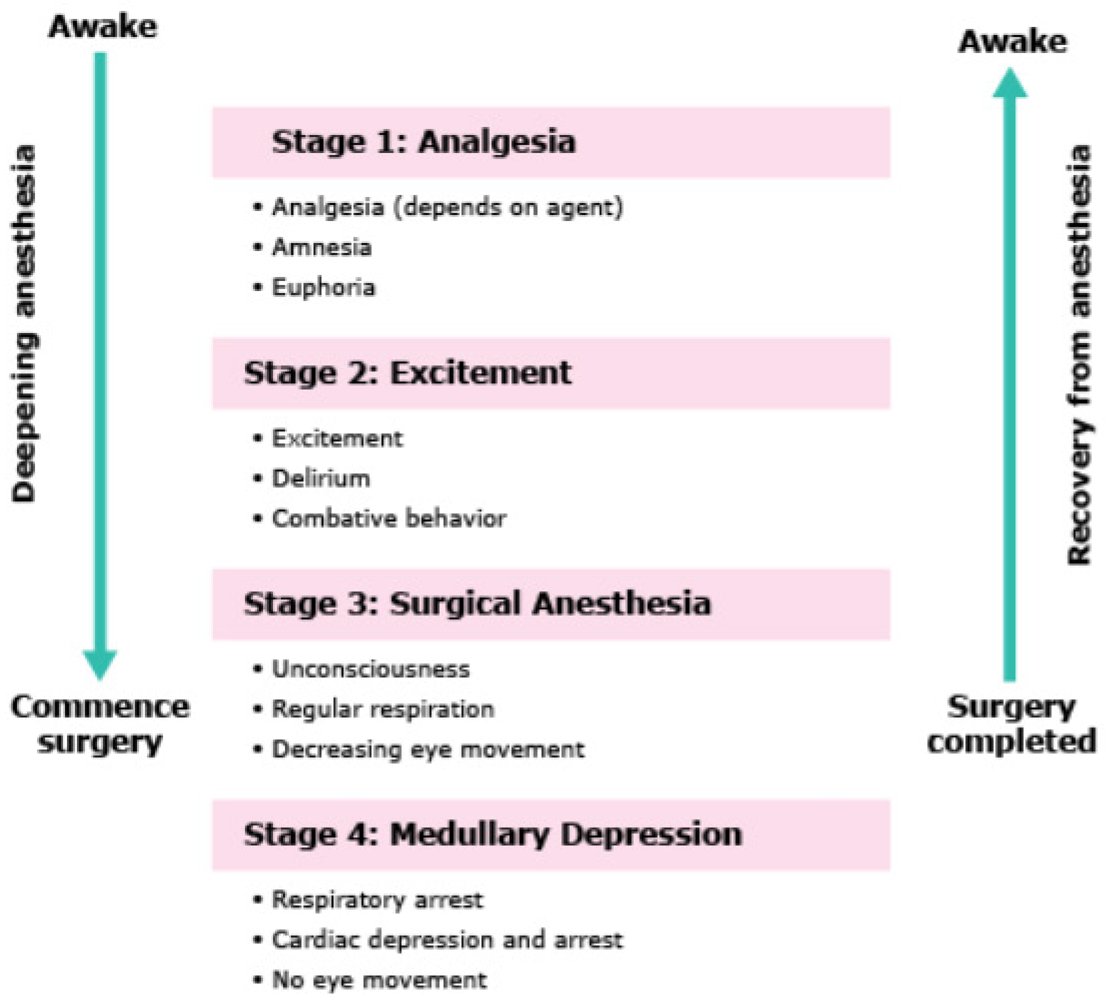
- Lorazepam
- Diazepam (sometimes given per rectum if unable to establish IV line)
- Fosphenytoin (water-soluble, can be infused rapidly)
- Phenytoin

4 Anesthetic Drugs

There are two main classes of anesthetic drugs: general anesthetics and local anesthetics. These drugs have very different mechanisms of action and clinical applications. Most general anesthetics work by enhancing GABA activity, especially at the inhibitory $GABA_A$ receptor. An exception is the dissociative general anesthetics such as ketamine. Local anesthetics inhibit voltage-gated sodium channels.

4.1 Stages of General Anesthesia

There are four main stages of general anesthesia. For surgical anesthesia, multiple medications often are used to avoid prolonged stage 2, an excitatory stage where patients can be combative and disoriented. Agents, such as thiopental or propofol, that provide rapid induction are useful in quickly progressing patients to stage 3 (surgical anesthesia). Stage 4 (medullary depression) is dangerous and must be avoided.


Awake
Deepening anesthesia
Commence surgery
Stage 1: Analgesia
• Analgesia (depends on agent)
• Amnesia
• Euphoria
Stage 2: Excitement
• Excitement
• Delirium
• Combative behavior
Stage 3: Surgical Anesthesia
• Unconsciousness
• Regular respiration
• Decreasing eye movement
Stage 4: Medullary Depression
• Respiratory arrest
• Cardiac depression and arrest
• No eye movement
Awake
Recovery from anesthesia
Surgery completed

▲ **Figure 4-4.1** Stages of General Anesthesia

4.2 Inhaled General Anesthetics

Inhaled anesthetics include nitrous oxide and halogenated ethers. Nitrous oxide should not be confused with nitric oxide, which is a self-signaling molecule that causes vasodilation and is given sublingually for angina. The newer, inhaled anesthetics include isoflurane, sevoflurane, and desflurane. These commonly are used in the operating room.

4.2.1 Minimal Alveolar Concentration (MAC)

The minimum alveolar concentration (MAC) is a measure of anesthetic potency defined as the concentration of vapor in the lungs that is able to prevent movement in 50% of patients in response to a surgical stimulus or pain. This is analogous to the ED50, but is measured as a concentration in the air. A higher MAC indicates lower potency.

MAC values are lowered by administration of other opioid analgesics. This is why fentanyl, a potent opioid analgesic, is often given with the general anesthetic—it allows less of the general anesthetic to be used in patients. For nitrous oxide, the MAC is 105% although for most other anesthetics, such as isoflurane, the MAC is about 1%. This means that nitrous oxide alone cannot be used as a complete anesthetic unless in a hyperbaric chamber. However, when administered at 70%, it can reduce the MAC of other anesthetics by about half.

4.2.2 Blood-Gas Partition Coefficient

Another important concept for general anesthesia is the blood/gas partition coefficient. This coefficient is a measure of the solubility of the anesthetic in the bloodstream compared to that in the lungs. A higher coefficient means that more of the inhaled anesthetic dissolves in the blood. Anesthetics cause their effect by acting in the brain, which is very fatty because of myelin. The more soluble an anesthetic is in blood, the longer it takes to exert action in the brain. The newest general anesthetic, desflurane, has very low blood solubility and has rapid onset of action.

4.3 Intravenous Drugs

Thiopental, propofol, and ketamine are the most commonly used intravenous anesthetics in use today. Thiopental and propofol both work by enhancing the activity of inhibitory $GABA_A$ receptors.

4.3.1 Thiopental

Thiopental is a lipid soluble barbiturate that is used at low doses for the induction and maintenance of anesthesia, and to lower intracranial pressure. It is commonly given intravenously for induction of general anesthesia to help move the patient past stage 2 of anesthesia.

It is important to remember that thiopental is lipid soluble, so it can be redistributed to fat mass. This can cause the hangover effect, which occurs when a drug persists in the body long after administration has ceased.

4.3.2 Propofol

Propofol (Diprivan) is commonly seen in operating rooms and in the intensive care unit. It is used for both induction and maintenance of general anesthesia. Propofol is poorly water soluble, therefore it is supplied as a milky lipid solution. Similar to thiopental, propofol can be redistributed to fat mass.

4.3.3 Ketamine

Ketamine is an intravenous general anesthetic commonly used for children. Ketamine works by noncompetitively antagonizing the NMDA glutamate receptor.

Ketamine causes an unusual form of general anesthesia known as dissociative anesthesia. This means that patients can sometimes have their eyes open and they can still move their muscles, but the drug itself is able to cause analgesia and amnesia. Ketamine is frequently used in emergent trauma to induce/maintain anesthesia, and maintain perfusion of the organs. It also can be used in remote settings because of minimal respiratory depression.

Adverse effects of ketamine are myoclonus, increased intracranial pressure, vivid dreams, and hallucinations. Children tolerate this drug better than adults. Ketamine is occasionally abused for its psychotropic effects. Ketamine is related to phencyclidine (PCP, or "angel dust"), which is a drug of abuse with a similar mechanism of action.

4.4 Local Anesthetics

The most commonly used local anesthetics include lidocaine, bupivacaine, and procaine. They are commonly used for regional anesthesia and nerve blocks. Regional anesthesia is produced by injecting one of these medications into either the epidural or subarachnoid space. Nerve block is produced by injection near a nerve bundle, which will affect a specific nerve, such as the pudendal nerve.

4.4.1 Pharmacokinetics

It is important to remember that local anesthetics are weak bases. In a physiological pH of approximately 7.4, about 1% to 10% of the molecules will be non-ionized. In order for these molecules to cross into the nerve membrane to exert their effect they have to be non-ionized. However, an infected tissue has a lower pH (usually about 5), so the number of non-ionized molecules drops to 0.1%. This makes it harder for that molecule to enter the nerve, inhibit sodium channels, and block propagation of nerve impulses. Consequently, infected tissues such as abscesses are hard to anesthetize.

The ester family of the local anesthetics includes procaine, cocaine, and bencyclane. These are metabolized by esterases in both the plasma and the tissue. The amide local anesthetics have an "i" in the first part of their names (ignore the "-caine" suffix), as you can see in lidocaine, bupivacaine, and mepivacaine. These are metabolized by liver amidases.

4.4.2 Adverse Effects

Adverse effects of local anesthetics include dizziness, nystagmus, sensory impairment, and seizures; especially when the medication such as lidocaine is inadvertently injected into an artery. Most of the local anesthetics suppress cardiovascular parameters except for cocaine.

4.5 Neuromuscular Blockers

Neuromuscular blockers are used during surgical anesthesia (stage 3 anesthesia) to cause muscle relaxation and immobility. It is very important to use a neuromuscular blocker during surgery so the patient does not move any muscles. Neuromuscular blockers work by blocking the nicotinic acetylcholine receptor at the neuromuscular junction. They are divided into two groups: nondepolarizing and depolarizing.

4.5.1 Nondepolarizing Neuromuscular Blockers

Nondepolarizing neuromuscular blockers are competitive antagonists at the skeletal muscle nicotinic acetylcholine receptor. Their action can be overcome by high concentrations of acetylcholine. The action of these medications can be reversed by acetylcholinesterase inhibitors, such as neostigmine.

Cholinesterase inhibitors also are known as reversal agents because they increase the concentration of synaptic acetylcholine, which will compete with and reverse the actions of nondepolarizing neuromuscular blockers. Nondepolarizing neuromuscular blockers can cause progressive paralysis, but they do not affect cardiac or smooth muscle and they do not alter consciousness. Therefore, patients who are not under general anesthesia should not receive these agents. The prototype medication is tubocurarine, which is isolated from the skin of a poison arrow frog.

Ken Lucas/Visuals Unlimited, Inc.

▲**Figure 4-4.5** Poison Arrow Frog

Mivacurium Mivacurium is commonly used in the United States for muscle relaxation during surgery or mechanical intubation. It is one of the more potent nondepolarizing neuromuscular blockers, and it has a very short duration of action because it is very quickly degraded by butyrylcholinesterase. This medication can cause allergic reactions associated with histamine release, which will cause hypotension, reflex tachycardia, and cutaneous flushing.

Pancuronium This steroid-based compound does not display hormone activity. It has a long duration of action, and it is not metabolized by the plasma cholinesterase. Pancuronium is more commonly used in longer surgeries because of its long duration of action.

Atracurium This agent has an intermediate duration of action, so it is usually used in shorter surgeries because patients can recover rapidly. It is inactivated in the plasma spontaneously. *Cis*-atracurium is atracurium modified such that it does not cause the adverse reaction of histamine release. A unique side effect of both of these drugs is CNS excitation and seizures caused by the breakdown product, laudanosine.

Vecuronium This is an aminosteroid, although it does not have hormone activity. It is one of the shorter-acting nondepolarizing blockers with a duration of action of approximately 30 to 40 minutes. It has very few side effects, and it is safe.

4.5.2 Depolarizing Neuromuscular Blockers

Depolarizing neuromuscular blockers are agonists at the nicotinic receptor. They work by persistently depolarizing the muscle cell, which makes it resistant to further stimulation from endogenous acetylcholine. Consequently, a physician will first observe fasciculations in the patient followed by flaccid paralysis.

The prototype depolarizing neuromuscular blocker is succinylcholine, a drug that is structurally related to acetylcholine. This agent has a very short duration of action because it is quickly inactivated by plasma cholinesterase. It is classically known to cause hyperkalemia because of the rapid depolarization of the muscle. This releases potassium from the cell into the bloodstream as sodium enters the cell. In rare cases, succinylcholine can cause malignant hyperthermia. It is important to remember that succinylcholine is *not* reversed by reversal agents, such as neostigmine.

4.5.3 Butyrylcholinesterase (Pseudocholinesterase) Deficiency

Deficiency of butyrylcholinesterease (also known as plasma cholinesterase or pseudocholinesterase) can affect succinylcholine and mivacurium, which rely on this enzyme for their degradation. About one in 5,000 Caucasians have the deficiency, which means that they can be paralyzed for hours until the drug is eliminated by other pathways.

4.6 Spasmolytics

Spasmolytics are medications that work by decreasing muscle tone and spasm. They can be very helpful in patients that have developed cerebral palsy or some injury to the spinal cord.

4.6.1 Baclofen

Baclofen works by activating the $GABA_B$ receptor, which is a metabotropic inhibitory GPCR. Baclofen will hyperpolarize neurons and muscle cells by activating potassium channels.

4.6.2 Dantrolene

Dantrolene is the antidote to malignant hyperthermia. Dantrolene works by blocking calcium release from the sarcoplasmic reticulum inside a muscle cell. This decreases the likelihood that the muscle will contract.

4.7 Malignant Hyperthermia

Malignant hyperthermia is an adverse effect of anesthesia or neuromuscular blockers, such as succinylcholine or halothane, which causes extreme muscle rigidity and hyperthermia. If a patient exhibits malignant hyperthermia, the patient needs to be cooled and dantrolene started immediately.

5 Opioids

Opioids are a large class of polypeptide molecules that receive their name from similarity to the opium alkaloid morphine. Endogenous opioids such as endorphin, enkephalin, and dynorphin are cleaved from the proprotein proopiomelanocortin (POMC). They cause analgesia, which is an increase in pain tolerance, a decrease in pain perception, and a decreased reaction to pain. Drugs that affect the opioid receptors are widely used in clinical medicine.

Opiates are drugs related to alkaloids found in the opium poppy. Morphine and codeine are naturally found in opium. Hydrocodone, heroin, oxycodone, and buprenorphine are examples of semisynthetic derivatives of opium alkaloids (e.g., heroin is made by acetylating morphine). There also are synthetic opioids that interact with opioid receptors but that have very different chemical structure from the opium alkaloids. Examples include fentanyl, meperidine, methadone, and propoxyphene. The term opioids is often used to refer to all drugs, opiate or synthetic opioids, affecting opioid receptors.

5.1 Opioid Receptors

Opioid receptors are GPCRs, and they are divided into multiple subtypes, including the mu (μ), delta (δ), and kappa (κ) receptors.

5.1.1 Mu Opioid Receptor

The μ receptor is named because it binds morphine, and it is the most important opioid receptor for pain control. The μ opioid receptor also causes physical dependence, respiratory depression, miosis, a reduction in GI motility, and euphoria.

5.1.2 Kappa Opioid Receptor

The κ receptor binds enkephalin, and it produces dysphoric symptoms, such as delirium and dissociation, in addition to analgesia and sedation.

5.1.3 Delta Opioid Receptor

The physiologic role of δ opioid receptors is not well understood. Activation produces some analgesia but not as much as activating μ receptors.

5.2 Abuse and Adverse Effects of Opioid Drugs

Opioids can cause a number of adverse effects, even when used appropriately. In addition, opioid abuse is very common. The last decade has seen a substantial increase in the abuse of prescription opiates (hydrocodone, oxycodone) while the abuse of heroin has leveled off. Acute overdose of opioids is a common presentation to the emergency department and constitutes a medical emergency.

5.2.1 Common Adverse Effects of Opioids

The most common adverse effects of opioids are respiratory depression, constipation (decreased peristalsis), nausea, and emesis.

5.2.2 Opioid Overdose

The characteristic triad of opioid intoxication is pinpoint pupils (miosis), respiratory depression, and a comatose state. Management includes supportive care and administration of opioid antagonists.

5.3 Opioid Antagonists

Opioid antagonists are used in cases of opioid overdose.

5.3.1 Naloxone

Naloxone (Narcan) is a full antagonist of the μ opioid receptor and the most widely used opioid antagonist. Naloxone is often used empirically in the emergency setting for patients where opioid ingestion is suspected. One risk of naloxone is triggering withdrawal symptoms in some patients who chronically use opioids.

5.3.2 Naltrexone

Naltrexone is an antagonist of the opioid receptors that has a longer duration of action than naloxone. Naltrexone only can be given parenterally, generally as a depot injection by a health professional. Naltrexone is approved for treatment of chronic alcoholism, where the suspected mechanism is reducing cravings by blocking endogenous opioid effects.

5.3.3 Methylnaltrexone

Methylnaltrexone is a recently developed opioid antagonist that does not penetrate the blood-brain barrier. Methylnaltrexone blocks the peripheral effects of opioids and is primarily intended to prevent constipation from chronic opioid use (e.g., in cancer patients).

5.3.4 Tolerance, Dependence, and Withdrawal Symptoms

The chronic use of opioids can result in both tolerance (requiring escalating doses to achieve the same effect) and dependence. Withdrawal from chronic use can produce a variety of symptoms that may be severe:

- Anxiety
- Lacrimation
- Rhinorrhea
- Sweating
- Yawning
- Goose bumps
- Hot or cold flashes
- Muscle cramps and spasms
- Gastrointestinal distress (vomiting and/or diarrhea)

5.4 Agonists

Opioid agonists are widely used for management of pain. Morphine is the prototype opiate, although several other opiates are currently used more frequently in the United States.

5.4.1 Morphine

Morphine is the prototype opiate analgesic. Morphine undergoes extensive first-pass metabolism in the liver, which generates the active metabolite morphine-6-glucuronide. Morphine also is the active metabolite of codeine.

5.4.2 Codeine

Codeine is a weak opiate but it is converted to morphine by the enzyme cytochrome P450 (CYP) 2D6. Poor metabolizers of CYP2D6 do not convert codeine to morphine, and hence experience little analgesic effect from codeine. In contrast, ultrarapid metabolizers of CYP2D6 may experience adverse effects from too rapid conversion of codeine to morphine. Codeine also is used as a cough suppressant (antitussive).

5.4.3 Oxycodone

Oxycodone is a semisynthetic opiate intended for the treatment of chronic pain. Oxycodone is formulated either by itself (OxyContin) or mixed with acetaminophen (e.g., Percocet). Oxycodone is one of the most commonly abused prescription medications. Addicts may grind up pills and snort or inject it to achieve intoxication.

5.4.4 Hydrocodone

Hydrocodone (Vicodin, Lortab) is the most commonly prescribed opioid in the United States. It is relatively short-acting and always formulated with acetaminophen or other NSAID. Unlike morphine and oxycodone, hydrocodone is a Schedule III and not a Schedule II controlled substance.

5.4.5 Fentanyl

Fentanyl is a very short-acting synthetic opioid that is approximately 100 times more potent than morphine (common doses are micrograms not milligrams). Fentanyl is widely used in surgical anesthesia and also for procedural sedation (e.g., used with midazolam for colonoscopy procedures). Fentanyl also is available as a transdermal patch for the treatment of chronic pain.

5.4.6 Meperidine

Meperidine (Demerol) is a synthetic opioid analgesic that is now less frequently used because of the popularity of hydrocodone and oxycodone. Meperidine can be converted to toxic metabolite normeperidine, which can cause seizures in meperidine overdoses.

5.4.7 Hydromorphone

Hydromorphone (Dilaudid) is a semisynthetic opiate analgesic commonly used in the hospital setting to manage acute pain.

5.4.8 Heroin

Heroin (diacetylmorphine) is synthesized by acetylating morphine isolated from poppy plants. Heroin is a Schedule I controlled substance in the United States, meaning that it is considered to have no legitimate medical use. Heroin often is injected intravenously, which is dangerous from the direct effects of the drug but also from other associated risks, such as infection from contaminated needles.

5.4.9 Methadone

Methadone is a long-acting synthetic opioid traditionally used in the treatment of opioid addiction. Methadone generates less of a high than drugs such as heroin but curbs the withdrawal symptoms and drug cravings. Methadone also is used in the management of chronic pain.

5.5 Partial Agonists

Opioid partial agonists are used in the management of opioid addiction. The rationale is to curb opioid withdrawal by providing some opioid activation but to block the ability of addicts to abuse full opioid agonists. When the opioid receptors are occupied by a partial agonist, the full efficacy of opioid agonists such as hydrocodone are prevented.

5.5.1 Buprenorphine

Buprenorphine is an opioid receptor partial agonist used in the treatment of opioid addiction. Buprenophine is formulated with naloxone in the combination drug Suboxone, which only can be prescribed by specially licensed physicians. Buprenorphine-naloxone is given sublingually such that the naloxone is not absorbed. If the patient attempts to abuse the product and inject intravenously, the naloxone will block any opioid effects.

5.6 Other Opioids

Opioids also are used for therapeutic reasons other than pain management, such as cough suppression or diarrhea. As mentioned previously, codeine is used for its antitussive properties.

5.6.1 Loperamide and Diphenoxylate

Loperamide (Imodium) and diphenoxylate (Lomotil) are opioids that do not penetrate the CNS. There are both used for the treatment of diarrhea.

5.6.2 Dextromethorphan

Dextromethorphan is a drug commonly found in cough suppressant over-the-counter medications. Although dextromethorphan has minimal adverse effects at intended doses, adolescents and young adults sometimes abuse large amounts (e.g., multiple bottles) of dextromethorphan to achieve a high. At high doses, dextromethorphan inhibits monoamine oxidase type B and can cause serotonin syndrome, especially if abused in someone taking selective serotonin reuptake inhibitors such as fluoxetine.

5.6.3 Tramadol

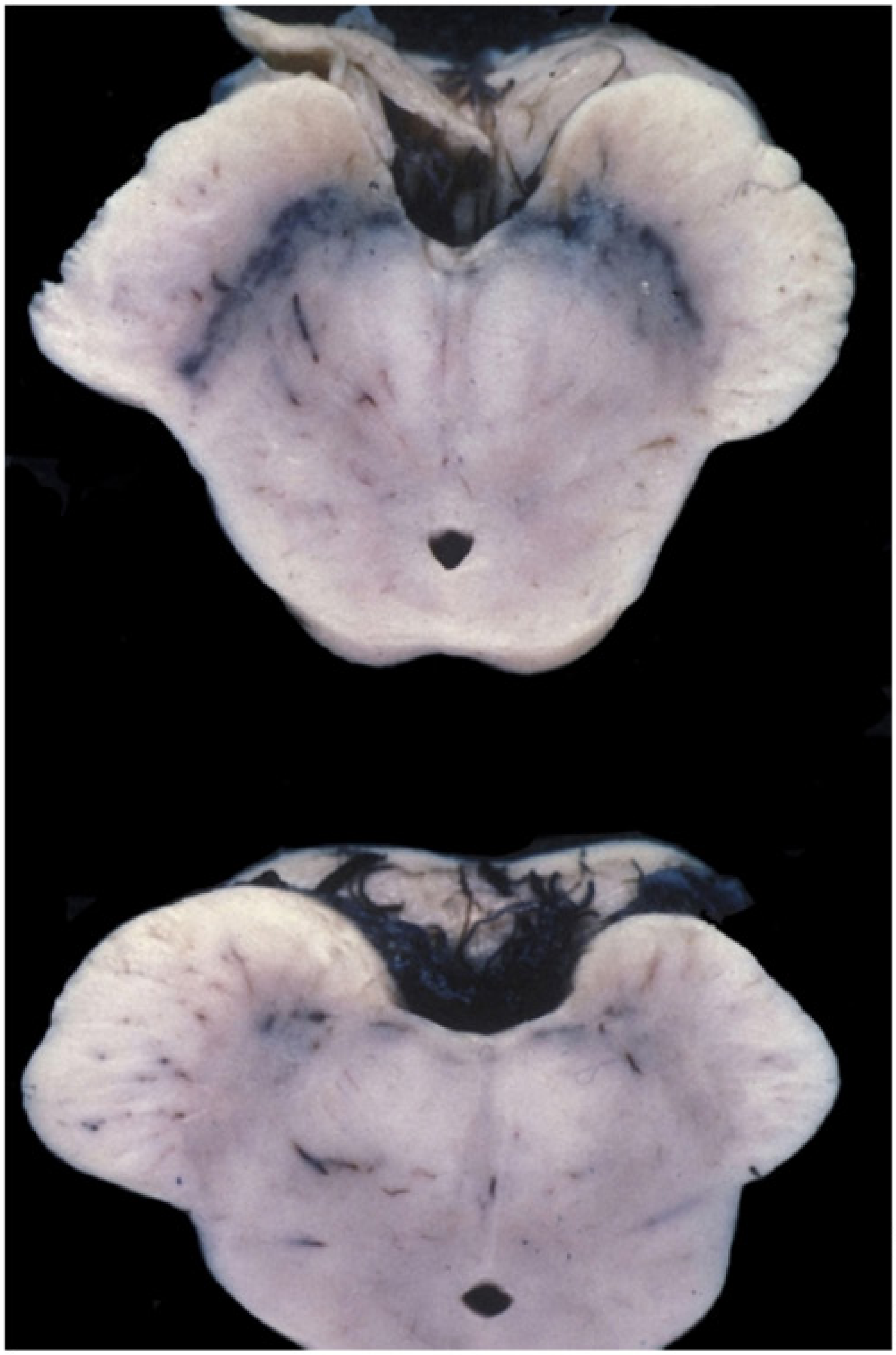
Tramadol is a weak opioid with very little abuse potential. Tramadol also causes increases in serotonin and norepinephrine levels. Tramadol is commonly given for severe pain in patients who cannot tolerate NSAIDs.

6 Parkinson Disease

Parkinson disease is characterized classically by a resting tremor, bradykinesia, muscular rigidity, postural instability, and masked facies. The goal of treatment is to manage the symptoms and improve patient mobility.

6.1 Pathophysiology

Parkinson disease results from degeneration of dopaminergic neurons in the substantia nigra and the striatum. The goal of therapy is to increase dopamine activity.



ISM/Phototake, Inc.

▲**Figure 4-6.1** Parkinson Disease

6.2 Levodopa-Carbidopa

L-dopa (levodopa) is a compound that is converted to dopamine by the enzyme dopa decarboxylase (also known as aromatic amino acid decarboxylase). Dopamine does not cross the blood-brain barrier and hence cannot be used for the treatment of Parkinson disease. Levodopa is considered first-line therapy for Parkinson disease. Its effect, however, has been shown to decline over 5 to 10 years of therapy. This decline in effectiveness may be due to the continual loss of dopaminergic neurons and/or to the large fluctuations in dopamine levels. Levodopa is almost always given with carbidopa, a drug that inhibits dopa decarboxylase in the periphery and thus prevents premature conversion to dopamine prior to levodopa crossing the blood-brain barrier.

The adverse effects of levodopa are related to fluctuations in dopamine levels, including "on-off effects," in which patients oscillate between dyskinesias (too much dopamine) and muscle rigidity (too little dopamine). Patients also may display psychotic symptoms, such as vivid dreams, disorientation, and confusion.

6.3 COMT inhibitors

Catechol-O-methyltransferase (COMT) is one of several enzymes that degrade catecholamines, including dopamine, epinephrine, and norepinephrine. Inhibition of COMT is one strategy for increasing dopamine levels in the brain. The most common use of COMT inhibitors in Parkinson disease is together with levodopa to achieve a more consistent therapeutic benefit.

Entacapone is an inhibitor of COMT that can be used on its own or with levodopa in Parkinson patients. Entacapone can minimize the on-off effects of levodopa.

6.4 Monoamine Oxidase Type B Inhibitors

Monoamine oxidase (MAO) type B catalyzes the enzymatic breakdown of dopamine. Similar to COMT inhibitors, MAO type B inhibitors are used in Parkinson disease treatment to boost dopamine levels in the brain.

6.4.1 Selegiline

Selegiline is a selective inhibitor of MAO type B, at least in the doses typically used in patients. It can be used on its own or together with levodopa in Parkinson patients.

At high doses, selegiline also inhibits MAO type A. Consequently, adverse interaction with tyramine-containing foods—such as cured or pickled meats, chocolate, alcoholic beverages, and fava beans—is possible in selegiline overdoses. Metabolism of selegiline produces L-amphetamine and L-methamphetamine, which can have sympathomimetic effects, although not as powerful as the more active D-amphetamine and D-methamphetamine isomers. The selegiline metabolites can produce positive amphetamine screens in drug tests.

6.4.2 Rasagiline

Rasagiline is an irreversible inhibitor of the MAO type B enzyme that has little activity at MAO type A. Rasagiline's therapeutic use is similar to that of selegiline.

6.5 Dopamine Agonists

Dopamine agonists are sometimes used in Parkinson disease therapy, although not nearly as often as levodopa. Dopamine receptor agonists are beneficial for treating Parkinson disease because, as a non-peptide, they do not compete with dopamine or other neutral amino acids for transport across the blood-brain barrier, and they are effective late in the progression of Parkinson disease.

6.5.1 Bromocriptine

Bromocriptine is a D_2 receptor used as an adjunct or alternative therapy to levodopa. Bromocriptine is not commonly prescribed due to dopamine-related adverse effects such as dyskinesias, hallucinations, and psychosis. Bromocriptine is sometimes used to treat hyperprolactinemia (prolactin release by the anterior pituitary is negatively regulated by dopamine).

6.5.2 Pramipexole and Ropinirole

Pramipexole and ropinirole are dopamine receptor agonists with more activity at D_3 than at D_2 receptors. These agents have fewer adverse effects than bromocriptine.

6.6 Muscarinic Antagonists

The loss of dopaminergic signaling in the basal ganglia leads to a relative excess of muscarinic signaling. Antimuscarinic agents that penetrate the blood-brain barrier are used to reduce the excessive cholinergic activity and reduce tremor and rigidity. The two most common antimuscarinic agents used in Parkinson disease are benztropine and trihexyphenidyl.

7 Schizophrenia

Schizophrenia is a mental disease characterized by problems with thought processes and emotional responsiveness. In a broad sense, there are two types of symptoms in schizophrenia: positive and negative.

- **Positive symptoms**: Thought disorders, paranoia, delusions, hallucinations, and bizarre behavior.
- **Negative symptoms**: Social withdrawal, flat affect (absence of emotional response), and poverty of speech.

The dopamine hypothesis states that schizophrenia symptoms result from too much dopamine activity in the brain although, clearly, other neurotransmitter systems are involved, as well.

7.1 Antipsychotics (Neuroleptics)

In the last 20 years, there has been a dramatic shift in the antipsychotics used in the United States. The older medications are often referred to as "typical antipsychotics" and include haloperidol, chlorpromazine, fluphenazine, and thioridazine. The newer medications are the "atypical antipsychotics" and include aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. The atypical antipsychotics have more diverse pharmacologic mechanisms and are the front-line therapy for schizophrenia, comprising more than 90% of prescriptions for antipsychotics in the U.S.

7.1.1 Mechanisms of Action

The typical antipsychotics are generally dopamine receptor antagonists, particularly for the dopamine-2 (D_2) receptor. However, these drugs also interact with several other receptors to cause adverse effects, as described as follows. Atypical antipsychotics have more diverse pharmacology, but many block dopamine-4 (D_4) and/or serotonin-2 ($5HT_2$) receptors.

7.1.2 Typical vs. Atypical Antipsychotics

The typical antipsychotics are generally good at treating the positive symptoms of schizophrenia but are not as effective for the negative symptoms. The atypical antipsychotics are much better than the typical agents at treating the negative symptoms, and also reduce the positive symptoms as well. The efficacy of atypical antipsychotics in managing positive and negative symptoms, in addition to better adverse effect profile, has led to these agents becoming front-line therapy.

7.2 Typical Antipsychotics

The typical antipsychotics are thought to exert their therapeutic effect mainly by blocking the D_2 receptor. However, they also block muscarinic acetylcholine receptors (causing atropine-like effects, such as dry mouth and urinary retention) and α-adrenergic receptors (causing postural hypotension, sexual dysfunction, and sedation). A discussion of additional adverse effects follows. Two of the typical antipsychotics (haloperidol and fluphenazine) are available in long-acting "depot" intramuscular injections, which can boost compliance.

7.2.1 Haloperidol

Haloperidol (Haldol) is the most commonly used of the typical antipsychotics. It also is used for the acute management of psychosis and mania, as well as for Tourette syndrome. It is less sedating than the other typical antipsychotics.

The side effects of haloperidol include dystonia, akathesia, gynecomastia, and Parkinsonism. It can also cause tardive dyskinesia and QT prolongation.

7.2.2 Chlorpromazine

Chlorpromazine blocks D_2 receptors, as well as muscarinic, α-adrenergic, and histaminergic receptors. Because of potential adverse effects, chlorpromazine is now used mainly for schizophrenia refractory to other therapies.

Chlorpromazine commonly is associated with obstructive jaundice and increased prolactin secretion resulting in gynecomastia. Chlorpromazine is classic for also causing a QT prolongation, which can lead to torsade de pointes and potentially life-threatening ventricular tachycardia. The drug carries an FDA black box warning for this potentially fatal adverse effect.

7.2.3 Thioridazine

Thioridazine (Mellaril) has similar pharmacology to chlorpromazine. Due to potential adverse effects, thioridazine is now used mainly for schizophrenia refractory to other therapies.

Thioridazine can cause retinal deposits, so regular ophthalmologic appointments that include retinal examination are recommended. Like chlorpromazine, thioridazine can prolong the QT interval and thus also has an FDA black box warning.

7.2.4 Fluphenazine

Fluphenazine (Prolixin) has similar pharmacology to haloperidol and is also available in a long-acting depot injectable form.

7.2.5 Adverse Reactions and Syndromes

The typical antipsychotics are associated with a number of potentially severe adverse reactions and syndromes.

Acute Dystonic Reaction These reactions involve muscle spasms that can occur in any muscle group:

- Oculogyric crisis (eye and face muscles)
- Blepharospasms (eyelid muscles)
- Torticollis (sternocleidomastoid muscles)
- Laryngospasm (airway)
- Trismus (jaw)

Depending on the muscle group, these spasms can be very dangerous. Acute dystonic reactions usually occur early in typical antipsychotic therapy and are thought to be due to an imbalance between dopaminergic and cholinergic signaling. In addition to aggressive supportive care, the pharmacologic management of acute dystonic reaction usually includes a muscarinic antagonist such as benztropine, trihexyphenidyl, or diphenhydramine.

Akathisia This presents as an inner feeling of restlessness combined with motor movements (patients "cannot sit still"). Akathisia can be confused with agitation or anxiety. This reaction can be managed by reducing the dose of the antipsychotic and, in the short term, by giving a β-blocker or benzodiazepine.

Parkinsonism Antipsychotics can produce Parkinson-like effects in patients due to a decrease of dopaminergic activity. The effects usually appear within days to weeks of starting antipsychotic therapy and are usually reversible by reducing the dose of antipsychotic agent and giving another drug with antimuscarinic effects.

Tardive Dyskinesia Often irreversible, tardive ("late appearing") dyskinesia is another complication of antipsychotic therapy. It is associated with drugs that have a high affinity for the D_2 receptor, and it usually occurs after prolonged treatment (years). Tardive dyskinesia is characterized by repetitive, stereotyped, involuntary movements of the face (typically grimaces and lip smacking), limbs, or trunk. The atypical antipsychotics cause tardive dyskinesia much less frequently than the typical agents.

Neuroleptic Malignant Syndrome This rare syndrome is quite similar in clinical presentation to malignant hyperthermia with extreme muscle rigidity, hyperthermia, cardiovascular instability, and altered level of consciousness. Like malignant hyperthermia, neuroleptic malignant syndrome is treated by aggressive supportive care and dantrolene. Bromocriptine (dopamine receptor agonist) is sometimes used, with the theory that this helps overcome the dopamine blockade of the antipsychotic.

7.3 Atypical Antipyschotics

The atypical antipsychotics are a newer and growing class of medications, which includes aripiprazole, clozapine, olanzapine, risperidone, sertindole, quetiapine, and ziprasidone. As a class, the medications are considered first-line therapy drugs of choice for the treatment of schizophrenia, and some also are formulated in long-acting intramuscular formulations. Although they are more effective at treating the negative symptoms of schizophrenia, most of the atypical antipsychotics (except for aripiprazole) are associated with weight gain. Atypical antipsychotics target receptors other than the D_2 receptors including the serotonin-2A (5-HT_{2A}) and D_4 receptors.

7.3.1 Risperidone

Risperidone (Risperdal) is one of the commonly used atypical antipsychotics. It is approved for treatment of schizophrenia in teenagers and adults, as well as for bipolar disorder and irritability in children with autism. Like most other atypical agents, risperidone is associated with weight gain.

7.3.2 Aripiprazole

Aripiprazole (Abilify) is a commonly used atypical antipsychotic that not only antagonizes the 5-HT_{2A} receptor but, unlike other agents, also acts as a partial agonist at the D_2, 5-HT_{1A}, and 5-HT_{2C} receptors. The different pharmacologic profile may underlie why aripiprazole does not cause weight gain. Aripiprazole is also approved for the treatment of bipolar disorder and acute mania.

7.3.3 Clozapine

Clozapine (Clozaril) is highly effective in treating schizophrenia but is limited by the adverse effect of agranulocytosis in about 1% of patients. Prescriptions of clozapine only are filled if there is evidence of regular monitoring of patient blood counters (a process known as "bundling"). Agranulocytosis typically occurs within the first several months of therapy. If it has not occurred by then, the risk drops off dramatically. Clozapine also is rarely associated with myocarditis.

8 Medications for Mood Disorders

The mood disorders include major depression and bipolar disorder. The medications used to treat these two types of mood disorders are mostly distinct.

8.1 Depression

Major depressive disorder (clinical depression) is commonly treated with a combination of both pharmacotherapy and psychotherapy. The combination therapy has been shown to be more effective than either one alone, although mild depression may respond well to either therapy. Electroconvulsive therapy (ECT) also has been shown to be effective (and arguably is underutilized due to negative publicity regarding this therapy). It is used for patients who are refractory to pharmacotherapy.

There are six main classes of antidepressants:

- Monoamine oxidase inhibitors (MAOIs)
- Tricyclic antidepressants (TCAs)
- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Tetracyclic antidepressants
- Other (bupropion, trazodone, St. John's wort)

A general feature of antidepressants is that onset of therapeutic effects takes weeks to months.

8.1.1 MAO Inhibitors

The MAOIs are an old, seldom-used class of antidepressants. The classic MAOIs are phenelzine and tranylcypromine, both of which inhibit MAO type A and B. MAOIs are effective for depression but, due to their adverse effects, are limited to the treatment of depression refractory to other therapies.

The major adverse effect of MAOIs is an interaction with tyramine-containing foods, such as cheese and wine. Inhibition of MAO interferes with the metabolism of tyramine, potentially leading to hypertensive crisis. MAOIs also should not be used in combination with SSRIs because of the risk of serotonin syndrome (discussed later).

8.1.2 Tricyclic Antidepressants

TCAs block reuptake of both norepinephrine and serotonin by the inhibition of norepinephrine and serotonin transporters. TCAs used to be the dominant class of antidepressants in the United States but now are used much less commonly than more selective drugs such as the SSRIs. Amitriptyline, clomipramine, imipramine, and nortriptyline are the classic TCAs.

Therapeutic Uses TCAs are still used for the treatment of major depression. However, they also are used for other indications, including:

- Obsessive-compulsive disorder (clomipramine)
- Enuresis (imipramine)
- Chronic pain (amitriptyline)

Amitriptyline is the most commonly prescribed TCA in the United States, largely due to the popularity of this drug in treating neuropathic pain.

Adverse Effects TCA overdose is very toxic and is considered a medical emergency. At high dose, TCAs inhibit α-adrenergic receptors, muscarinic acetylcholine receptors, and histamine receptors. Patients who overdose on TCAs can develop arrhythmias, have decreased reflexes, respiratory depression, and ultimately become hypotensive and comatose. Amitriptyline overdose can resemble atropine poisoning because of the powerful muscarinic blockade. Withdrawal from TCAs or stopping it too quickly—that is, without a taper—can cause major symptoms as well as increased blood pressure and agitation. TCAs should not be given concurrently with MAOIs or SSRIs because of the risk of serotonin syndrome.

8.1.3 Specific Serotonin Reuptake Inhibitors

The discovery of SSRIs in the 1980s and 1990s was a major advance in the treatment of depression. These medications have much fewer side effects compared to the other classes of antidepressants (e.g., TCAs, MAOIs). SSRIs, such as fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft), are first-line treatment for clinical depression. These medications selectively block the serotonin transporter, which increases the concentration of serotonin in the synaptic cleft.

Important Concept

Overdose of monoamine oxidase inhibitors or tricyclic antidepressants is much more dangerous than overdose of selective serotonin reuptake inhibitors.

Therapeutic Uses SSRIs are indicated for use in major depression, anxiety states such as panic disorders, social phobias, premenstrual dysphoric disorder, obsessive-compulsive disorders, eating disorders, and other mood or behavioral disorders.

Adverse Effects Sexual dysfunction, such as difficulty in achieving orgasm, anxiety, agitation, and insomnia, are adverse effects associated with SSRIs. If SSRIs are stopped too quickly, they can cause a withdrawal syndrome.

8.1.4 Serotonin-Norepinephrine Reuptake Inhibitors

The selective serotonin-norepinephrine inhibitors (SNRIs) include venlafaxine (Effexor) and duloxetine (Cymbalta). In addition to treating major depression, duloxetine is also commonly used to treat neuropathic pain. The adverse effects are similar to SSRIs and additionally can cause sweating.

8.1.5 Tetracyclic Antidepressants

The tetracyclic antidepressants include mirtazapine (Remeron). Mirtazapine inhibits the presynaptic α_2-adrenergic receptor as well as serotonin receptors 2A, 2C, and 3. Inhibition of the presynaptic α_2-adrenergic receptor increases the release of serotonin and norepinephrine from the presynaptic terminal. One of the main advantages of mirtazapine is faster onset of action (days instead of weeks).

The most common adverse effects of mirtazapine include sedation, increased appetite, and weight gain. The latter side effect is sometimes used to advantage in treating elderly, underweight patients for depression.

8.1.6 Bupropion

Bupropion (Wellbutrin) is an antidepressant structurally related to amphetamine that inhibits dopamine and norepinephrine reuptake. It is frequently added onto first-line SSRI therapy, and it does not cause sexual dysfunction or increase weight. Bupropion also is marketed for smoking cessation (under the different tradename Zyban).

Bupropion has been associated with seizures and should not be used in patients with a history of epilepsy.

8.1.7 Trazodone

Trazodone is an atypical antidepressant that primarily acts as a serotonin-2 receptor antagonist. Trazodone is frequently used as a sleep aid, often in combination with SSRIs to offset the insomnia associated with SSRIs.

A rare adverse effect associated with trazodone is priapism (painful sustained erection), a complication that can be a medical emergency.

8.1.8 St. John's Wort

St. John's wort is an herbal antidepressant. The most active component is hyperforin, a compound whose pharmacology most closely resembles the selective serotonin-norepinephrine inhibitors like venlafaxine and duloxetine.

As described in chapter 1, St. John's wort is an inducer of multiple cytochrome P450 (CYP) enzymes. This can produce drug-drug interactions such as unintended pregnancy due to rapid metabolism of ethinyl estradiol in oral contraceptives ("St. John's wort babies").

8.1.9 Serotonin Syndrome

Serotonin syndrome is caused by an excess of serotonin. The most frequent causes are a combination of two or more drugs that affect different aspects of serotonin metabolism, for example, combining an MAOI (inhibiting an enzyme that breaks down serotonin) with an SSRI or TCA (blocking transporter reuptake of serotonin). In addition to antidepressants, some other drugs can cause serotonin syndrome. Examples include dextromethorphan or meperidine, which at overdose levels can inhibit MAO.

The symptoms of serotonin syndrome include diaphoresis, muscular rigidity, convulsions, and autonomic instability, characterized by hypertension and tachycardia. Serotonin syndrome is considered a medical emergency and is managed by external cooling, supportive care, intravenous benzodiazepines, and sometimes cyproheptadine (serotonin receptor antagonist).

8.2 Bipolar Disorder

The treatment of bipolar disorder is much more difficult than the treatment of depression. Even though depression is part of the clinical presentation of bipolar disorder, the use of an antidepressant can worsen the disease by swinging the patient toward more severe manic episodes. The prototype drug for bipolar disorder is lithium. A recent trend is the use of some anticonvulsants and antipsychotics for the management of bipolar disorder. The drugs used to treat bipolar disorder are often referred to as mood stabilizers.

8.2.1 Lithium

Lithium was the first successful medication for bipolar disorder. Although clinically effective, adverse effects of lithium are frequent and can be difficult to manage.

Mechanism of Action Lithium works by changing the balance of cyclic AMP and inositol triphosphate (IP_3) inside the cell. The exact mechanism of action of lithium is poorly understood. Lithium can act like a sodium ion and interact with some sodium channels, although these interactions probably have relation mainly to adverse, not therapeutic, effects.

Adverse Effects Lithium can produce a range of adverse effects:

- Tremors
- Scotomas (seeing spots)
- Leukocytosis
- Headache
- Weight gain
- Hypothyroidism
- Nephrogenic diabetes insipidus
- Teratogenicity in first trimester (Ebstein's anomaly of tricuspic valve)

Plasma levels of lithium are usually monitored closely to avoid toxic concentrations. Because lithium is cleared by the kidneys, patients with renal insufficiency especially need close monitoring. Overdose of lithium can be life-threatening and may include ataxia, cardiac arrhythmias, and coma.

Clinical Application

In contrast to central diabetes insipidus (e.g., hypothalamic or pituitary injury leading to a lack of ADH secretion), nephrogenic diabetes insipidus is an inability to respond to ADH. Lithium-induced diabetes insipidus can be managed by amiloride.

8.2.2 Other Medications Used for Bipolar Disorders.

In addition to lithium, a number of other medications are used as mood stabilizers. These include drugs traditionally classified as anticonvulsants or antipsychotics:

- Valproic acid
- Carbamazepine
- Lamotrigine
- Olanzapine
- Aripiprazole
- Risperidone

9 Drugs With Stimulant Properties

A number of drugs with CNS stimulant properties are used therapeutically or may be abused. Examples include amphetamine, cocaine, and methylphenidate.

9.1 Cocaine

Cocaine is a powerful peripheral and CNS stimulant. Cocaine has a narrow therapeutic use as a local anesthetic for eye and nose surgeries (hence the regulation as a Schedule II and not a Schedule I controlled substance). Cocaine is commonly abused by inhalation or intravenous injection.

9.1.1 Mechanism of Action

Cocaine inhibits the dopamine and norepinephrine transporters, leading to increased levels of these neurotransmitters in the autonomic and central nervous systems. Cocaine also blocks voltage-gated sodium channels like other local anesthetics. Cocaine is advantageous for some eye and nasal surgeries because of its ability to produce both local anesthesia (by blocking voltage-gated sodium channels) and vasoconstriction (by increasing norepinephrine levels). The euphoric effects of cocaine are produced largely by the dopaminergic effects in the brain.

9.1.2 Adverse Effects

When abused, cocaine can produce vasoconstriction, tachycardia, and cardiac arrhythmias. The leading causes of cocaine-related death are myocardial infarction, stroke, and arrhythmias. Cocaine abuse increases the lifetime risks of cerebral aneurysm rupture. Cocaine abuse during pregnancy can lead to increased risk of spontaneous abortion, placental abruption (detachment of the placenta from the lining of the uterus), and premature labor.

9.1.3 Management of Cocaine Overdose

There is no specific antidote for cocaine overdose. Management of overdose includes supportive care and administration of labetalol to reduce the adrenergic effects.

9.2 Amphetamine and Amphetamine-Like Drugs

Amphetamines encompass a group of CNS stimulants that include amphetamine, methamphetamine, and MDMA ("Ecstasy"). There also are designer drugs that are amphetamine-like, some of which are referred to by misleading names such as "bath salts."

9.2.1 Mechanism of Action

Amphetamines increase dopamine and norepinephrine release from nerve terminals. The dopamine effects can produce psychosis-like symptoms that resemble schizophrenia.

9.2.2 Amphetamine

D-Amphetamine is the more pharmacologically active of the two amphetamine isomers. A racemic mixture of amphetamines (Adderall or its generic equivalent) is commonly used to treat attention-deficit hyperactivity disorder (ADHD). Paradoxically, stimulant drugs like amphetamine are beneficial in ADHD, likely by improving focus and concentration. Amphetamine also is used in the treatment of narcolepsy.

9.2.3 Methamphetamine

D-Methamphetamine ("meth") is a common drug of abuse. Methamphetamine can produce an intense high and strong dependence. Methamphetamine use can lead to a variety of destructive behaviors and also severe damage to teeth. The production of methamphetamine in small "meth labs" can be quite dangerous and lead to toxic chemical exposure (including to children) and fires.

9.2.4 MDMA/Ecstasy

3,4-Methylenedioxy-N-methamphetamine (MDMA, Ecstasy) is a drug of abuse classically associated with the underground culture (e.g., rave parties). MDMA can produce a variety of adverse effects including teeth grinding, hallucinations, and hyperthermia.

9.2.5 Other Amphetamine-Like Drugs

There is a large group of amphetamine-like drugs that occasionally surface as drugs of abuse. Examples include drugs distributed with the misleading name of "bath salts" (e.g., methylone; methylenedioxypyrovalerone/MDPV). These drugs can have their own unique pharmacologic profile but in general have stimulant properties.

9.3 Ephedrine and Pseudoephedrine

Ephedrine and pseudoephedrine are closely related drugs that activate α- and β-adrenergic receptors. Ephedrine was used in unregulated dietary supplements (e.g., Metabolife, *Ma-huang*) until removed from the U.S. market by the FDA in 2004. Pseudoephedrine (e.g., Sudafed) is used therapeutically as a decongestant. There are some restrictions on purchasing (e.g., need to show identification) to prevent diversion of pseudoephedrine to make methamphetamine.

9.4 Medications Used to Treat ADHD

In addition to amphetamine, methylphenidate and atomoxetine are used to treat ADHD.

9.4.1 Methylphenidate

Methylphenidate (Ritalin, Concerta) is an inhibitor of the dopamine and norepinephrine transporters. Methylphenidate is commonly used to treat ADHD.

9.4.2 Atomoxetine

Atomoxetine (Strattera) is a selective norepinephrine reuptake inhibitor used to treat ADHD. The use of atomoxetine has declined because of associations with increased blood rate, heart arrhythmias, and liver damage. These adverse effects prompted an FDA black box warning.

Review Questions Chapters 3–4

The following vignette applies to questions 1 and 2.

A 47-year-old male manager at a printing supply company presents for evaluation of "high cholesterol" levels found during a recent physical examination with laboratory studies. His HDL cholesterol is 25 mg/dL (normal > 45), LDL cholesterol is 240 mg/dL (normal 60-180), and total cholesterol is 280 mg/dL (normal < 200 mg/dL). The physician places him initially on lovastatin to reduce his LDL cholesterol and raise his HDL cholesterol. The patient is maintained on lovastatin for several months with a modest decrease of his LDL cholesterol. His physician then places him on another drug in addition to the lovastatin for better therapeutic effect. After 10 days on the combination of drugs, the laboratory tests show further improvement; however, the patient complains of facial flushing and itching on the lower back, palms, and buttocks.

1. What second drug was he *most likely* placed on?

A. Gemfibrizol
B. Probucol
C. Cholestyramine
D. Nicotinic acid
E. Clofibrate

2. In addition to periodically monitoring the patient's cholesterol panel, what other laboratory tests should be monitored regularly in this patient if he remains on the two drugs?

A. Platelet count
B. Alanine aminotransferase
C. Erythrocyte count
D. Thyroid stimulating hormone
E. Serum lactic acid

The following vignette applies to questions 3 and 4.

A pregnant woman in her second trimester is having problems with chronic hypertension. So far, the hypertension is not severe, but concern exists because her previous pregnancy was complicated by preeclampsia.

3. What drug would be the *most appropriate* for hypertension management of this patient?

A. Sodium nitroprusside
B. Captopril
C. Aliskerin
D. Losartan
E. α-Methyldopa

4. The same patient presents in the 38th week of labor with a blood pressure of 230/120 mmHg. She complains of vision impairment. In addition to clinically indicated obstetric management, what drug is *most appropriate* for treating this patient's hypertensive emergency?

A. Reserpine
B. Sodium nitroprusside
C. Candesartan
D. Hydralazine
E. Enalapril

Chapters 3–4 Review Questions

5. A 65-year-old male with congestive heart failure and hypertension takes digoxin and hydrochlorothiazide. Which of the following laboratory tests should be *most closely* monitored?

A. Platelet count
B. Plasma sodium
C. Alanine aminotransferase
D. Plasma potassium
E. Serum albumin

6. Which of the following diuretics would be the *best agent* for management of a 40-year-old female with moderate essential hypertension?

A. Furosemide
B. Acetazolamide
C. Spironolactone
D. Mannitol
E. Hydrochlorothiazide

7. A 35-year-old man visits your office for advice on dealing with insomnia associated with occasional night-shift work. He only would take medications for less than a week at a time to help him fall asleep. Which of the following medications is *most appropriate?*

A. Secobarbital
B. Diazepam
C. Zolpidem
D. Chloral hydrate
E. Propofol

8. A 33-year-old female has received treatment that ameliorated delusions and auditory hallucinations. More recently, however, she has been withdrawn and shows little change in emotion. What is *most likely* to be appropriate therapy at this time?

A. Phenytoin
B. Haloperidol
C. Risperidone
D. Trazadone
E. Thioridazine

Review Questions Chapters 3–4

9. A 25-year-old man is brought to the emergency department by his parents because of severe muscle spasms in his neck. With twisting of his head to the right, he has sustained spasm of the sternocleidomastoid and trapezius muscles. You learn from his father that he was started on haloperidol for schizophrenia four days earlier. The *most appropriate* pharmacotherapy at this time is:

A. Trihexphenidyl
B. Risperidone
C. Prochlorperazine
D. Diazepam
E. Phenytoin

The following vignette applies to questions 10 and 11.

A 12-year-old boy is doing poorly in school. At multiple times during the day, he is observed to "go blank" for 10 to 20 seconds and be unresponsive to questions from teachers. Afterward, he is slightly confused but returns to normal within 10 seconds. EEG monitoring reveals a spike and wave pattern during one of these episodes lasting about 20 seconds.

10. What *most likely* would be appropriate pharmacotherapy for this patient?

A. Phenobarbital
B. Carbamezapine
C. Diazepam
D. Ethosuximide
E. Fosphenytoin

11. If the child experienced severe nausea and vomiting after taking your choice above, what would be the *best* second choice?

A. Propofol
B. Gabapentin
C. Lorazepam
D. Methylphenidate
E. Valproic acid

Chapters 3–4 Review Questions

12. A 25-year-old male with a history of paranoid schizophrenia has been maintained on an antipsychotic drug for five years. Recently, he has developed skeletal muscle rigidity, a resting tremor, flat facies, and uncontrollable restlessness. On which of the following neuroleptics has he *most likely* been maintained?

A. Risperidone
B. Clozapine
C. Haloperidol
D. Olanzapine
E. Quetiapine

13. A mother brings her 9-year-old son to the pediatrician because of increasing behavioral problems in school. The boy's teacher states that the child cannot sit quietly through a class and frequently disrupts students. The mother says that her son has always been active ("like he was driven by a motor") and has been to the emergency room numerous times for injuries sustained by "carelessness." The most appropriate pharmacotherapy for this child *most likely* increases brain levels of which neurotransmitter?

A. Serotonin
B. Neurokinin
C. Epinephrine
D. Acetylcholine
E. Dopamine

14. A patient taking tranylcypromine for major depression experiences symptoms of overdose after consuming a large meal that includes fava beans and Chianti wine. What is the *most likely* physical sign that will result from an adverse reaction?

A. Respiratory rate of 5 breaths/min
B. Blood pressure of 240/120 mmHg
C. Serum potassium of 2 mEq/L
D. Platelet count of 10 k/mm3
E. Blood pH of 6.9

Review Answers Chapters 3–4

1. The correct answer is D. Nicotinic acid (niacin) not only is an essential water-soluble B vitamin but also an effective treatment for hypercholesterolemia when given in high doses (2–6 g/day). These doses of nicotinic acid rapidly decrease LDL and VLDL cholesterol levels and also result in an increase in HDL cholesterol levels. Although effective, these high doses of nicotinic acid also cause numerous side effects, including intense flushing and pruritus, which generally involve the upper body and face. These effects sometimes subside over time. The other major side effect is *abnormality of hepatic function*, which necessitates the periodic monitoring of liver function tests.

2. The correct answer is B. Alanine aminotransferase (a marker of liver damage) should be followed for patients on statin and nicotinic acid due to potential hepatotoxicity of these drugs. Statins and nicotinic acid have little effect on blood count, thyroid function, or lactic acid levels, so the monitoring of platelet count, erythrocyte count, thyroid function, and serum lactic acid would not be indicated.

3. The correct answer is E. α-Methyldopa is one of the drugs with a solid safety record for treatment of mild to moderate hypertension in pregnancy. The ACE inhibitors and angiotensin II receptor antagonists are both associated with teratogenicity and oligohydramnios (deficiency of amniotic fluid). Aliskerin would be predicted to also cause problems in pregnancy due to similarity to ACE inhibitors. Sodium nitroprusside only is reserved for very severe hypertension, and the possibility of cyanide and thiocyanate poisoning makes it an undesirable choice in pregnancy.

4. The correct answer is D. Of the choices, *hydralazine* is the best option for management of severe hypertension in pregnancy. Sodium nitroprusside also is used for severe hypertension but the possibility of cyanide and thiocyanate poisoning causes safety worries in pregnancy. Enalapril (ACE inhibitor) and candesartan (an angiotensin II receptor antagonist) are associated with teratogenicity and oligohydramnios. Reserpine would not be used for the acute management of severe hypertension.

5. The correct answer is E. Hypokalemia increases the effectiveness of cardiac glycosides such as digoxin. Hydrochlorothiazide tends to cause hypokalemia so the plasma potassium should be carefully monitored in patients receiving such a combination of medication. Hyperkalemia leads to less digoxin effect. Changes in plasma sodium or in platelet levels have little effect on digoxin.

6. The correct answer is E. Hydrochlorothiazide is the first-line agent for essential hypertension. Furosemide generally would be reserved for more severe hypertension or a patient with congestive heart failure. Acetazolamide is uncommonly used for hypertension management. Spironolactone would not be first-line therapy in a patient with essential hypertension. Mannitol would not be used for outpatient management of hypertension.

7. The correct answer is C. Zolpidem. This is an appropriate indication for zolpidem (Ambien), a short-acting, non-benzodiazepine hypnotic. Secobarbital and chloral hydrate are older sedative/hypnotics with low therapeutic indices and more potential for adverse effects. Chloral hydrate is sometimes used for sedating children, particularly before procedures such as MRI. Diazepam (Valium) is a long-acting benzodiazepine and not appropriate as a short-term sleep aid. Propofol (Diprivan) is intended for hospital use only.

8. The correct answer is C. Risperidone. Symptoms in schizophrenia can be classified as "positive" (e.g., delusions, hallucinations) or "negative" (e.g., withdrawal, apathy). "Atypical" antipsychotics, such as risperidone (Risperdal), aripiprazole, quetiapine, and zipasidone, are thought to be more effective in treating negative symptoms than traditional antipsychotics such as haloperidol (Haldol) or thioridazine (Mellaril). Phenytoin and trazodone are not used in the management of schizophrenia.

Chapter 3–4 Review Answers

9. The correct answer is A. Trihexphenidyl. This patient is having an acute dystonic reaction, commonly seen within one week of starting a high-potency antipsychotic agent such as haloperidol (Haldol). This adverse effect is an emergency and may present as facial grimacing, torticollis (contracted cervical muscles), or oculogyric crisis and often is terrifying to patients. The treatment is an agent with central antimuscarinic (anticholinergic) actions such as benztropine (Cogentin) or trihexphenidyl (Artane).

10. The correct answer is D. Ethosuximide is first-line therapy for absence (petit mal) seizures, which this child most likely has. Absence seizures are often mistaken for ADHD. It may look like the child is not paying attention due to ADHD when in fact he or she is having seizures. The other choices are used for management of partial or tonic-clonic, but not absence, seizures. Other drugs commonly used for absence seizures are valproic acid, clonazepam, and lamotrigine. Ethosuximide and valproic acid are the most effective of these choices.

11. The correct answer is E. Valproic acid is appropriate alternative therapy for absence seizures. Other possibilities would be clonazepam or lamotrigine. Propofol is a general anesthetic and would not be used for managing absence seizures. Gabapentin is mostly used for the treatment of chronic pain. Lorazepam is used for the acute management of tonic-clonic seizures. Methylphenidate is used for the management of attention-deficit hyperactivity disorder.

12. The correct answer is C. Haloperidol is a so-called typical antipsychotic. Tardive dyskinesia is a late-appearing neurological syndrome associated with the use of neuroleptics, particularly with the typical D_2 antagonists, but to a smaller degree with the atypical D_2/5-HT_2 antagonists. Symptoms of tardive dyskinesia include stereotypical, repetitive, painless, involuntary, quick choreiform (tic-like) movements of the face, eyelids, mouth, tongue, extremities, or trunk. Symptoms usually persist indefinitely, even after discontinuation of the offending drug. The exact incidence of tardive dyskinesia is not known with newer antipsychotics such as quetiapine and olanzapine, but it probably is lower.

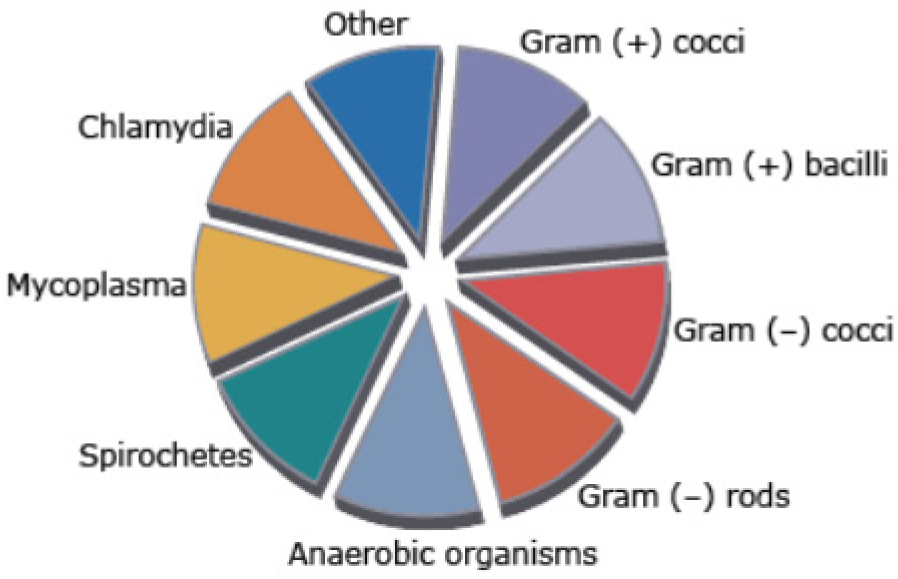
13. The correct answer is E. Dopamine. This is a classic history for attention-deficit hyperactivity disorder, for which methylphenidate (Ritalin), amphetamine mixed salts (Adderall), or atomoxetine (Strattera) are first-line therapies. Agents used to treat ADHD in general increase levels of the neurotransmitter dopamine.

14. The correct answer is B. Blood pressure of 240/120 mmHg. This is an example of a severe hypertensive crisis provoked by the consumption of tyramine-rich foods—for example, beer, fava beans, aged cheese, or red wine—in patients treated with a monoamine oxidase inhibitor (MAOI), such as tranylcypromine. With gastrointestinal and hepatic MAO inhibited, large quantities of tyramine from these foods can reach the circulation and trigger massive release of norepinephrine leading to life-threatening hypertensive crisis. The clinical use of MAOI involves dietary restrictions against the digestion of foods and drinks containing tyramine. Monoamine oxidase inhibitors are no longer as commonly used but this classic adverse drug reaction is a favorite of the boards.

CHAPTER 5 Antimicrobial Agents

1 Overview of Antimicrobials

Antimicrobial agents comprise a diverse array of compounds used to combat the microorganisms responsible for infectious disease. These agents can be classified by the various microorganisms they target. Antibacterials, of course, fight bacteria. Other antimicrobial treatments fight mycobacteria, fungi, viruses, and parasitic organisms.



▲ **Figure 5-1.0** Medically Important Microorganisms

Antimicrobials are a high-yield topic for Step 1. Areas of focus include:

- **Minimum Inhibitory Concentration (MIC):** MIC is the lowest concentration of a drug needed to inhibit bacterial growth in vitro. Stronger bacteriostatic agents have lower MICs, which differ from organism to organism. *Minimum bactericidal concentration (MBC)* is the lowest concentration of a drug needed to kill 99.9% of microorganisms in a colony count.
- **Combination Therapies:** Antimicrobials used in combination can have one of three outcomes:
  - **Synergistic:** Effects of the two agents in combination together multiply their therapeutic effect or one agent enhances the action of another normally inactive against the target organism (for example, aminoglycosides, normally inactive against gram-positive organisms, are used together with a penicillin or cephalosporin to treat *Enterococcus* infections).
  - **Additive:** Effects of the two agents summate (for example, ciprofloxacin and metronidazole to treat aerobic and anaerobic gut flora).
  - **Antagonistic:** Two agents interfere with each other (for example, tetracyclines and penicillin cannot be administered concurrently because of their chelation to one another).

USMLE® Key Concepts

For Step 1, you must be able to:

- Describe the mechanism of action of antimicrobials.
- Explain the various classes of antimicrobials and the clinical circumstances appropriate for each.
- Describe the common resistance mechanisms of microorganisms.
- List the adverse effects for specific antimicrobial agents.

- **Resistance Mechanisms:** Antimicrobial resistance is a growing problem in clinical settings. Bacteria can have spontaneous mutations that lead to resistance, which can then be transferred between bacteria by the sharing of plasmids. Change in the protein targeted by the drug can lead also to resistance, as seen in penicillin-binding proteins in the bacterial cell wall resulting in penicillin resistance. Decreased cellular permeability also may alter the channels the agent uses to enter the cell. Bacteria also can also increase efflux of drugs by upregulation of pump proteins that move the drug out of the cell. Finally, bacteria may increase expression of enzymes such as β-lactamases that inactivate antibiotics.
- **Adverse Effects:** Antimicrobials may exert direct toxicity, including organ damage, as with aminoglycosides causing nephrotoxicity and auditory nerve damage. Some classes of antibiotics, such as penicillins and sulfonamides, can induce hypersensitivity reactions. Some antibiotics inhibit or induce cytochrome P450 enzyme activity, potentially leading to interactions with other drugs.

2 Antibacterials

Although the terms *antibacterial* and *antibiotic* were traditionally used synonymously, the spectrum of activity for antibiotics has grown to include more than just bacteria, so this chapter uses antibacterials to describe those agents administered to treat bacterial infections. Mycobacteria will be covered separately in the next section.

2.1 Classification

Antibacterials can be classified in a number of ways. In Step 1, three forms of classification are studied: by intended effect, spectrum of activity, and mechanism of action.

2.1.1 Bactericidal vs. Bacteriostatic

Classification by intended effect divides antibacterials into two classes. *Bactericidal* agents kill bacteria; these agents do not require host immune response to combat an infection. Examples of bactericidal agents include penicillins and cephalosporins (which disrupt cell wall synthesis) and daptomycin, fluoroquinolones, and metronidazole. *Bacteriostatic* agents slow or stop bacterial growth, but do not destroy bacteria on their own—host immune response is typically required for that. Examples of these agents include tetracyclines and macrolides, which inhibit protein synthesis.

Important Concept

Bactericidal agents are preferred over *bacteriostatic* agents in most clinical situations involving severely ill or immunocompromised patients.

2.1.2 Narrow-Spectrum and Broad-Spectrum Agents

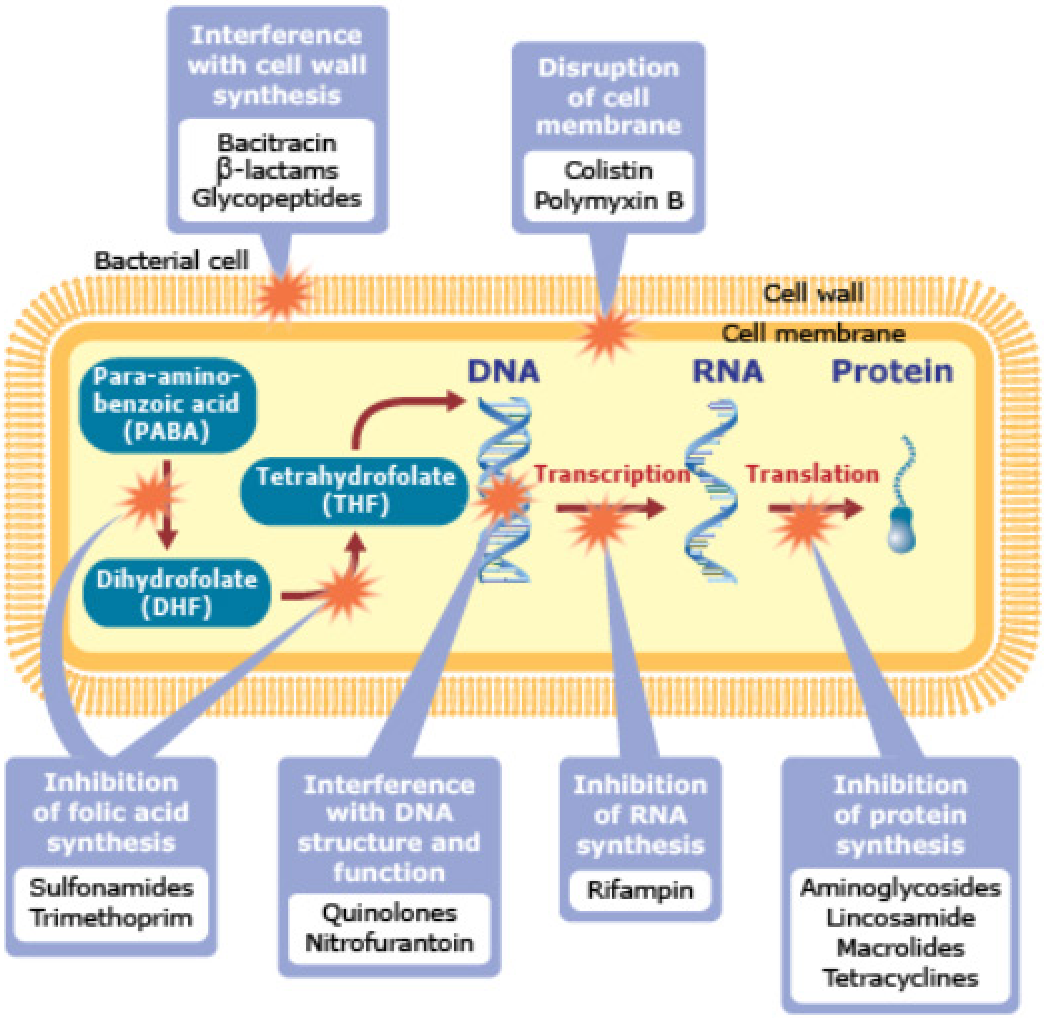
Classification of antibacterials based on spectrum of activity also divides agents into two groups. *Narrow-spectrum* agents combat a single or limited group of bacteria, as with isoniazid, which is active only against mycobacteria. *Broad-spectrum* agents are effective against a wide variety of bacteria. This is useful in severe infections, but carries the risk of disrupting normal bacterial flora in the host. Some antibacterials are active only against gram-positive bacteria (for example, vancomycin) and others are active only against gram-negative (for example, aminoglycosides).

2.1.3 Mechanism of Action

Classification by mechanism of action divides antibacterials into the following groups:

- Cell wall synthesis inhibitors
- Protein synthesis inhibitors
- Folic acid synthesis inhibitors
- Nucleic acid disruptors
- Cell membrane disruptors

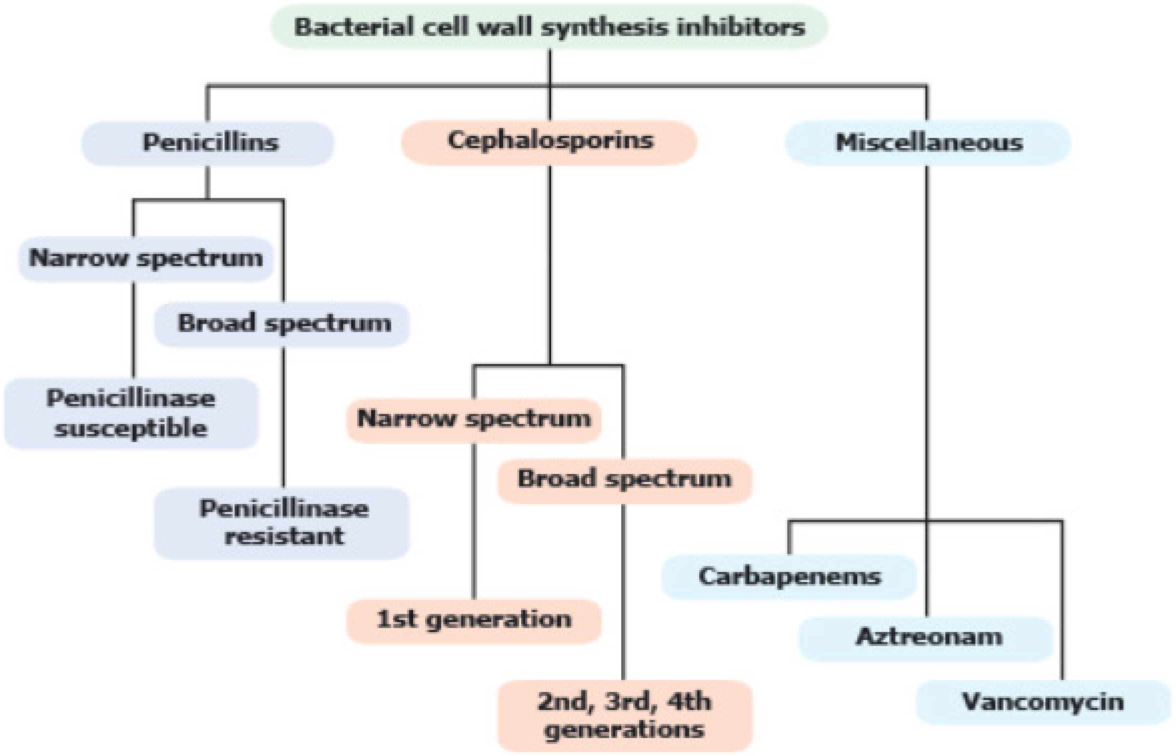
For Step 1, it is important to know the general features of these classes and the commonly used drugs within each.


Interference with cell wall synthesis
Bacitracin
β-lactams
Glycopeptides
Disruption of cell membrane
Colistin
Polymyxin B
Bacterial cell
Cell wall
Cell membrane
Para-amino-benzoic acid (PABA)
Tetrahydrofolate (THF)
Dihydrofolate (DHF)
DNA
RNA
Protein
Transcription
Translation
Inhibition of folic acid synthesis
Sulfonamides
Trimethoprim
Interference with DNA structure and function
Quinolones
Nitrofurantoin
Inhibition of RNA synthesis
Rifampin
Inhibition of protein synthesis
Aminoglycosides
Lincosamide
Macrolides
Tetracyclines

▲ **Figure 5-2.1** Antibacterial Mechanisms of Action

2.2 Cell Wall Synthesis Inhibitors

As their name suggests, these bactericidal agents target the cell walls of bacteria. This group includes penicillins, cephalosporins, aztreonam, carbapenems, and vancomycin.

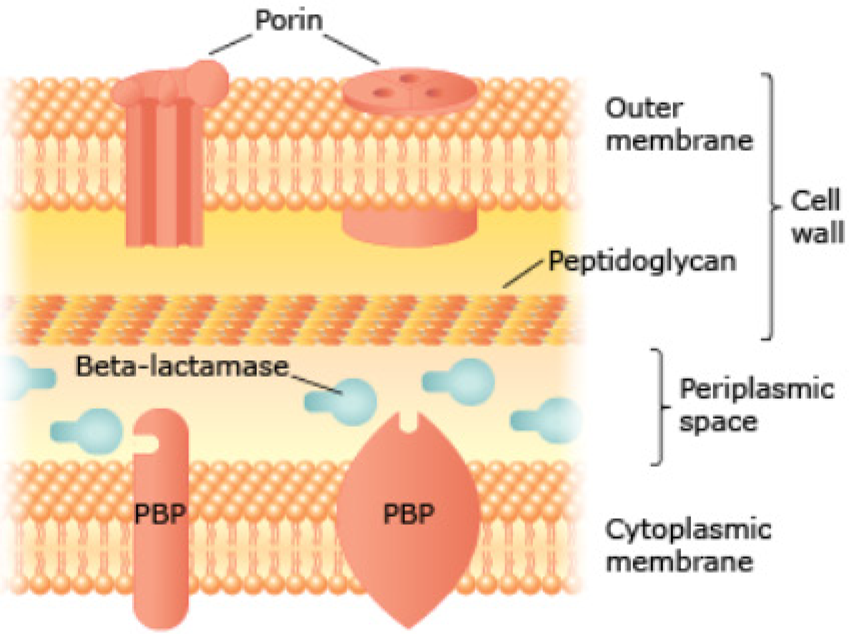

Bacterial cell wall synthesis inhibitors
Penicillins
Cephalosporins
Miscellaneous
Narrow spectrum
Broad spectrum
Penicillinase susceptible
Penicillinase resistant
Narrow spectrum
Broad spectrum
1st generation
2nd, 3rd, 4th generations
Carbapenems
Aztreonam
Vancomycin

▲ **Figure 5-2.2A** Cell Wall Synthesis Inhibitors

2.2.1 Penicillins

The penicillins are widely used bactericidal agents that target the bacterial cell wall.

Mechanism of Action Penicillins prevent formation of peptidoglycan cross-bridges in the cell wall by binding to penicillin-binding proteins (PBPs). Penicillins require actively proliferating microorganisms to be effective.


Porin
Outer membrane
Cell wall
Peptidoglycan
Beta-lactamase
Periplasmic space
PBP
PBP
Cytoplasmic membrane

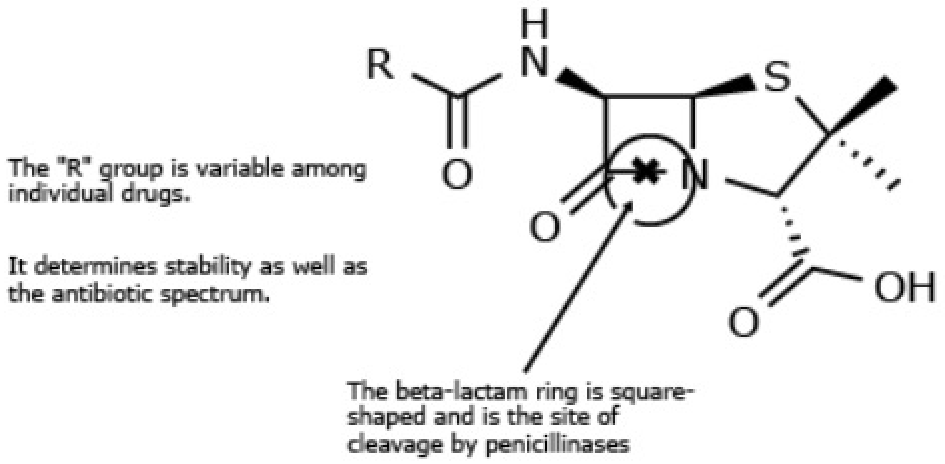
▲**Figure 5-2.2B** Beta-Lactams and Cell Wall Synthesis

Pharmacokinetics Most penicillins are excreted unmetabolized in the kidney by filtration and secretion. Exceptions are nafcillin, oxacillin, and dicloxacillin, which undergo biliary excretion.

Resistance Mechanisms The four mechanisms of resistance to penicillins are:

1. Degradation by bacterial penicillinases (also known as β-lactamases).
2. Mutation of PBPs to weaken penicillin binding.
3. Downregulation of porins that allow entry of penicillins.
4. Upregulation of efflux channels.

β-lactamases cleave the four-membered lactam ring.


R
H
N
S
N
O
O
O
OH
The "R" group is variable among individual drugs.
It determines stability as well as the antibiotic spectrum.
The beta-lactam ring is square-shaped and is the site of cleavage by penicillinases

▲**Figure 5-2.2C** Beta-Lactam Ring

Spectrum of Activity The spectrum of activity varies depending on agent (see below).

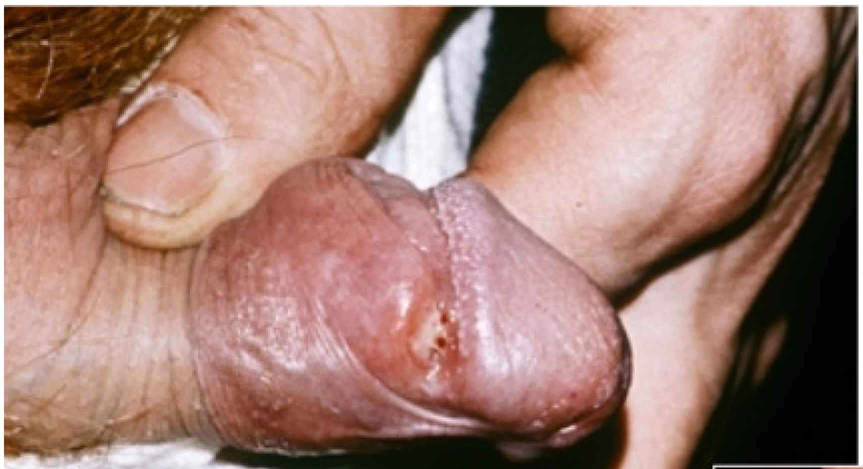
Adverse Effects Penicillins can cause *hypersensitivity reactions*. True type I anaphylactic reactions are rare (< 0.05%). Penicillins may also induce type III hypersensitivity reactions, such as serum sickness.

Penicillin Additives Some drugs are coadministered with penicillins to enhance activity by preventing resistance or slowing down excretion.

- **Beta-lactamase inhibitors:** These additives are competitive inhibitors of bacterial lactamases and include clavulanic acid, sulbactam, and tazobactam.
- **Probenecid:** This additive blocks the secretion of penicillins into urine and prolongs half-life.

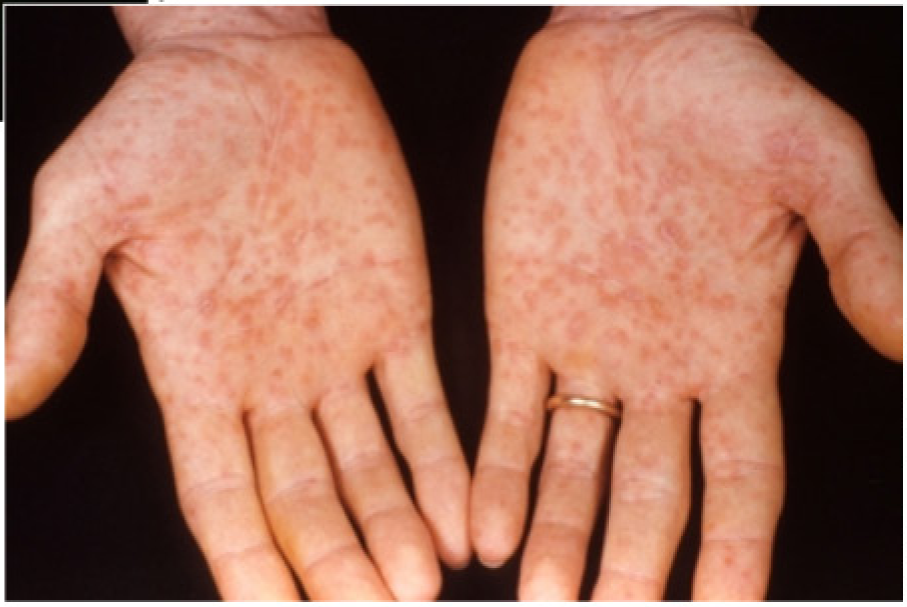
Narrow-Spectrum Penicillins These are rarely used due to antibiotic resistance, but do have niche applications.

- **Penicillin G (benzylpenicillin):** Penicillin G is used mainly for *syphilis*, as this bacteria has not shown resistance to this agent. Otherwise, very few bacteria are susceptible to penicillin G. Historically, it was used for *Neisseria meningitidis*, but this use has faded due to resistance. Ceftriaxone is a better choice for Step 1 questions concerning *N. meningitidis* infection.
- **Penicillin V:** Penicillin V is used to treat Group A *Streptococcus* infection.



Watney Collection/Phototake, Inc.

▲**Figure 5-2.2D** Primary Syphilis Lesion



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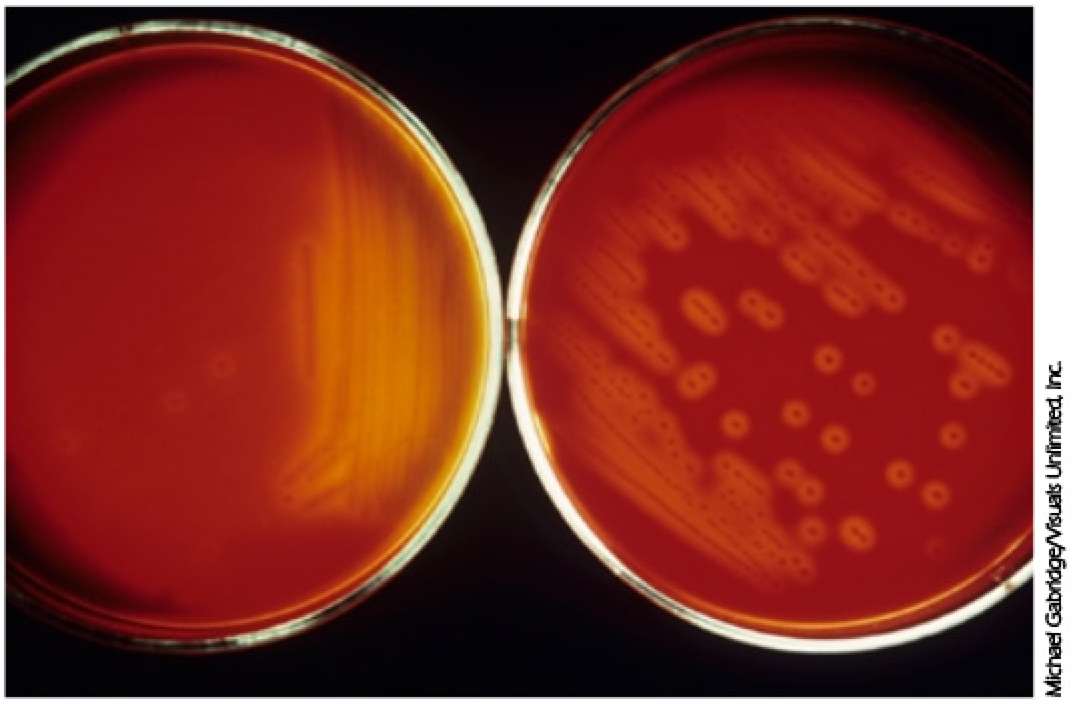
▶**Figure 5-2.2E** Secondary Syphilis



Michael Gabridge/Visuals Unlimited, Inc.

▲ **Figure 5-2.2F** *Streptococcus pyogenes* (Group A Strep)

Ampicillin This is an aminopenicillin with *"extended-spectrum"* action against gram-positive and gram-negative organisms. Mainly administered intravenously for gram-negative infections, ampicillin may be used empirically for suspected *Listeria meningitis* in infants and patients over 50 years old. The drug also covers *E. coli* and *Proteus*. Ampicillin causes a benign, *nonallergic reaction* when given during certain viral illness such as infectious mononucleosis. The drug may be coadministered with the β-lactamase inhibitor sulbactam.

Amoxicillin This is another extended-spectrum aminopenicillin. Amoxicillin has excellent oral absorption and is often used for otitis media, community-acquired pneumonia, and sinusitis. Amoxicillin may be given with the β-lactamase inhibitor *clavulanic acid*.

Important Concept

Combination therapy of amoxicillin and clavulanic acid is the clinically preferred prophylactic treatment for dog bites.

Penicillinase-Resistant Penicillins Some of the penicillins are intrinsically resistant to the action of β-lactamases.

- **Methicillin:** This is the prototype penicillinase-resistant penicillin. Methicillin is no longer used clinically due to risk of *interstitial nephritis*. However, laboratory testing commonly uses methicillin to detect whether *Staphylococcus aureus* is sensitive to penicillinase-resistant penicillins or resistant to methicillin ("methicillin-resistant *Staph aureus,*" or MRSA).
- **Oxacillin and Nafcillin:** These penicillinase-resistant penicillins are very similar and are commonly used to treat methicillin-sensitive *Staph aureus*.
- **Dicloxacillin:** This agent is commonly used to treat skin infections and mastitis (breast infection), which are commonly caused by staphylococcus species.

Important Concept

The main options for treatment of MRSA are vancomycin, linezolid, and quinupristin-dalfopristin.

Antipseudomonal Penicillins The antipseudomonal penicillins have activity against *Pseudomonas aeruginosa*.

- **Carboxypenicillins (Carbenicillin, Ticarcillin):** These agents are commonly used to treat methicillin-sensitive *Staph aureus* and some gram-negative infections such as *Pseudomonas* and *Klebsiella.*

- **Ureidopenicillins (Piperacillin):** Piperacillin is the most potent antipseudomonal penicillin and is combined with tazobactam (β-lactamase inhibitor).

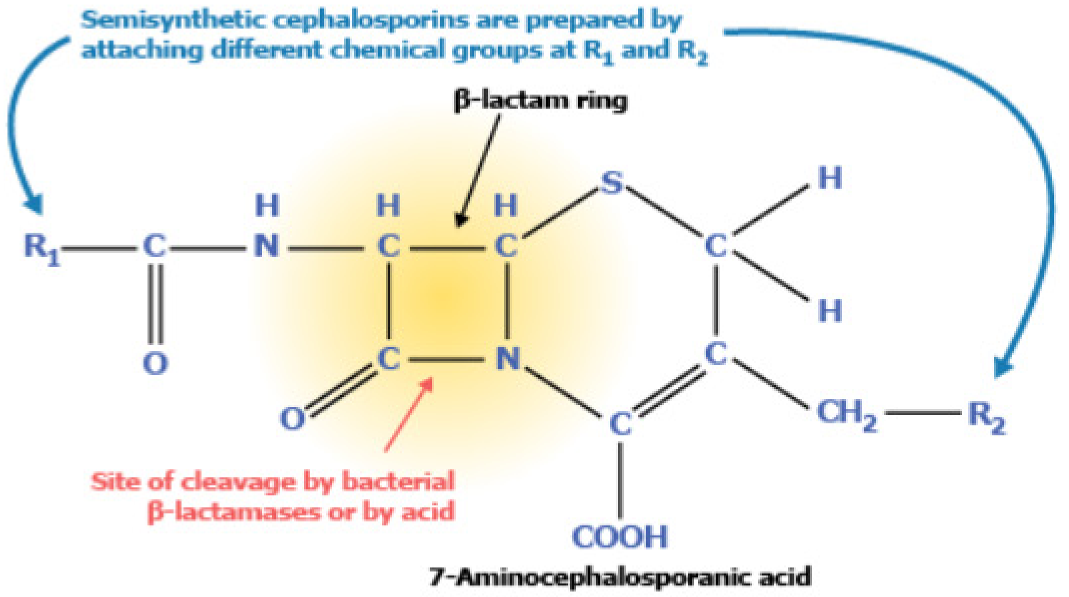
2.2.2 Cephalosporins, Carbapenems, and Monobactams

Cephalosporins, carbapenems, and monobactams all target bacterial cell wall synthesis. Cephalosporins are widely used clinically.

Mechanism of Action Cephalosporins have a similar mechanism of action to penicillins and are bactericidal.

Pharmacokinetics Cephalosporins are generally excreted unmetabolized by the kidney.

Resistance Mechanisms Cephalosporins have more resistance to standard β-lactamases than penicillins. However, a recent concerning development is the expression of extended-spectrum β-lactamases by gram-negative organisms.


Semisynthetic cephalosporins are prepared by attaching different chemical groups at R1 and R2
β-lactam ring
R1
C
O
H
N
H
C
H
C
S
C
H
H
C
O
N
C
C
CH2
R2
COOH
Site of cleavage by bacterial β-lactamases or by acid
7-Aminocephalosporanic acid

▲**Figure 5-2.2G** Cephalosporin Chemical Structure

Spectrum of Activity The cephalosporins are often divided into four generations based on their activity against gram-negative organisms. First- and second-generation agents have limited activity against gram-negatives, and third- and fourth-generation agents have greater activity against gram-negatives. Remember that the increase in cephalosporin generation does not imply lesser activity against gram-positives.

- **First-Generation Cephalosporins:** Cephalexin and cefazolin are the most commonly used, often as a prophylaxis for cellulitis before surgery.
- **Second-Generation Cephalosporins:** Cefuroxime, cefoxitin, and cefotetan have good activity against gram-positive cocci and also *Haemophilus influenzae* and *Enterobacter.*
- **Third-Generation Cephalosporins:** Ceftriaxone, cefotaxime, and cefixime are widely used in clinical settings due to good activity against gram-negatives—including those resistant to other agents—and nosocomial infections. Ceftriaxone is drug of choice for treatment of gonorrhea and meningococcal meningitis. Ceftazidime has antipseudomonal activity. Third-generation agents are not effective against gram-negatives expressing extended-spectrum β-lactamases (ESBLs).

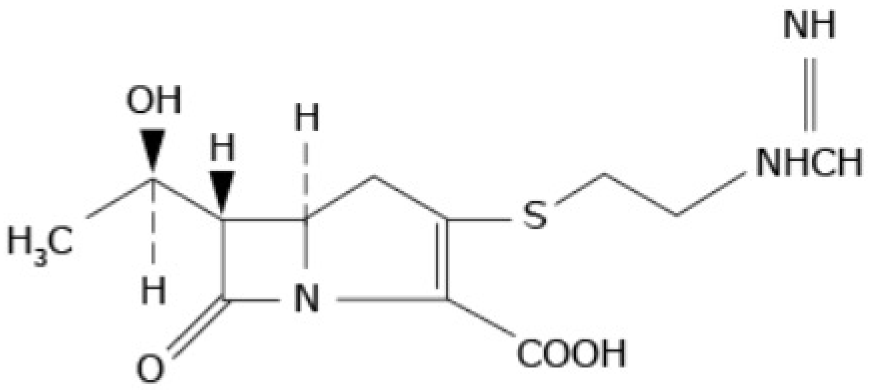
Important Concept

Ceftriaxone is the agent of choice for adults presenting with ***suspected meningitis***.

- **Fourth-Generation Cephalosporins:** Cefepime, an option for treating *Enterobacter*, *Klebsiella*, and *Pseudomonas*, has even more extended action against gram-positive and gram-negative organisms than third-generation agents.

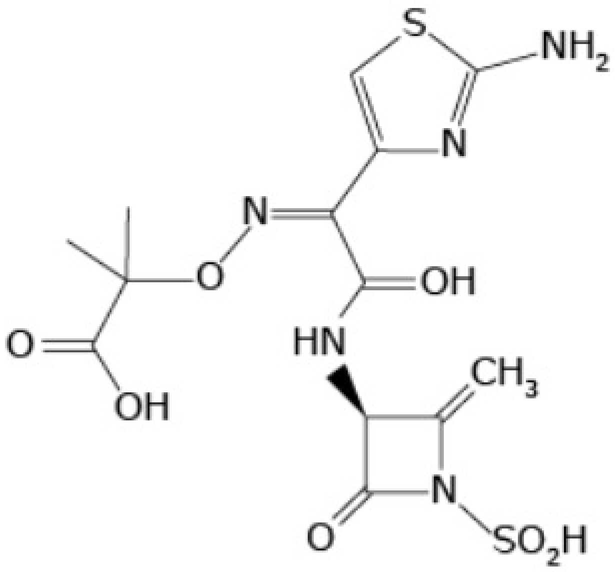
Adverse Effects Like penicillins, cephalosporins can cause hypersensitivity reactions. Classically, 10% of patients with life-threatening allergic reaction to penicillins also are allergic to cephalosporins.

Carbapenems (Imipenem, Meropenem, and Doripenem) Imipenem, meropenem, and doripenem are carbapenems that share similar mechanism of action, pharmacokinetics, and side effects, including *cross-allergenicity,* to penicillins. An additional effect is an increasing likelihood of seizures, especially with meropenem. These agents have a very broad spectrum of action and are usually restricted to use in hospitals for treatment of serious infections such as *necrotizing pancreatitis*. Imipenem is formulated with cilastatin, which prevents hydrolysis of imipenem by renal dihydropeptidase.



▲**Figure 5-2.2H** Structure of Imipenem

Monobactams (Aztreonam) Aztreonam is a monobactam antibiotic with weak activity against gram-positives but excellent activity against *gram-negative rods,* including those that produce *ESBLs*. Aztreonam has few side effects and virtually no cross-allergenicity to penicillins or cephalosporins.

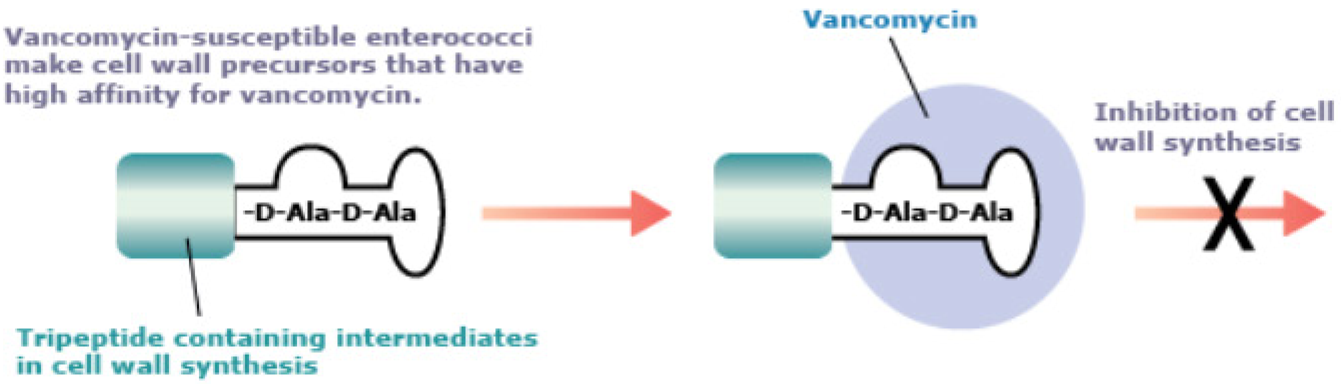


▲**Figure 5-2.2I** Structure of Aztreonam

2.2.3 Glycopeptide (Vancomycin)

Vancomycin is a glycopeptide antibiotic mainly used to treat *gram-positive* bacterial infections.

Mechanism of Action Vancomycin interferes with the bacterial cell wall by binding to D-alanyl-D-alanine moieties (D-Ala-D-Ala), thereby *inhibiting transpeptidation*. Like other antibacterials that target the cell wall, vancomycin is bactericidal.


Vancomycin-susceptible enterococci make cell wall precursors that have high affinity for vancomycin.
Vancomycin
Inhibition of cell wall synthesis
-D-Ala-D-Ala
-D-Ala-D-Ala
X
Tripeptide containing intermediates in cell wall synthesis

▲**Figure 5-2.2J** Vancomycin Action on *Enterococci*

Pharmacokinetics Vancomycin is poorly absorbed from the gastrointestinal tract and is usually administered intravenously. An exception is oral administration of vancomycin for *Clostridium difficile* colitis *(pseudomembranous colitis),* where absorption is not required.

Resistance Mechanisms Gram-negative organisms are intrinsically resistant to vancomycin due to their outer cell membrane. Gram-positive bacteria may acquire resistance by altering cell wall components from *D-Ala-D-Ala* to *D-Ala-D-Lac*. Vancomycin cannot bind this modified residue. Vancomycin-resistant enterococci *(VRE)* is an increasing health problem, especially in hospitalized patients.

Spectrum of Activity Vancomycin is used almost exclusively for gram-positive organisms, particularly those not easily treated by other antibacterials, including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermiditis*, and enterococci. Vancomycin may be given as prophylaxis prior to or during high-risk surgeries and procedures.

Adverse Effects The main acute adverse effect of vancomycin is known as *"red man syndrome"* and involves an erythematous rash on face and upper torso along with a drop in blood pressure. Red man syndrome is *mediated by histamine release* from mast cells and is most common when vancomycin is infused too quickly. Slow infusion and premedication with diphenhydramine can lessen symptoms. Vancomycin can rarely cause *ototoxicity* or *nephrotoxicity*. This is related to high plasma levels or the combined use of vancomycin with other nephrotoxic or ototoxic agents such as the aminoglycosides.

2.2.4 Lipopeptide (Daptomycin)

Daptomycin is a novel lipopeptide antibiotic with a similar spectrum of action to vancomycin, including predominant activity against gram-positive bacteria.

Mechanism of Action Daptomycin forms pores in the bacterial membrane and disrupts bacterial membrane potential. Daptomycin is bactericidal.

Pharmacokinetics Daptomycin is administered intravenously due to poor oral absorption.

Resistance Mechanisms Bacterial resistance to daptomycin has so far been minimal.

Spectrum of Activity Daptomycin is predominantly used to treat *MRSA* and *vancomycin-resistant enterococci*.

Adverse Effects Daptomycin rarely causes myopathy (similar to statins).

▼Table 5–2.2 Cell Wall Synthesis Inhibitors

Subclass	Activity Spectrum & Clinical Uses	Pharmacokinetics & Interactions	Toxicities
Penicillins ***Narrow spectrum*** *Penicillinase-susceptible* Penicillin G Penicillin V	Streptococcal and meningococcal infections; syphillis	Rapid renal elimination; short half-lives necessitate frequent dosing; some biliary clearance of nafcillin and oxacillin	Hypersensitivity reactions (~5%–6% incidence); ***assume complete cross-reactivity;*** GI distress and maculopapular rash (ampicillin)
Penicillinase-resistant Nafcillin Oxacillin	Staphylococcal infections		
Broad spectrum (+/−) penicillinase inhibitor Ampicillin Amoxicillin Piperacillin Ticarcillin	Greater activity vs. gram-negative bacteria All penicillins (and cephalosporins) are bactericidal		
Cephalosporins ***First-generation*** Cephalexin, others	Skin, soft tissue UT infections	Oral use for older drugs Mostly IV for newer drugs; renal elimination Short half-lives Third-generation drugs enter CNS	Hypersensitivity reactions (~2% incidence); ***assume complete cross-reactivity between cephalosporins; partial with penicillins;*** GI distress
Second-generation Cefotetan Cefoxitin Cefuroxime	More active vs. *S. pneumoniae* and *H. inflenzae;* *B. fragilis* (cefotetan)		
Third-generation Ceftriaxone Cefotaxime Ceftazidime	Many uses including ***pneumonia, meningitis,*** and ***gonorrhea***		
Fourth-generation Cefipime	Broad activity, beta-lactamase-stable		
Carbapenems Imipenem-cilastatin Meropenem Ertapenem	Broad spectrum includes some PRSP strains (not MRSA), gram-negative rods, and *Pseudomonas* sp.	Parenteral; cilastatin inhibits renal metabolism of imipenem; renal elimination	Partial cross-reactivity with penicillins; CNS effects include confusion and seizures
Monobactams Aztreonam	Active only vs. ***gram-negative*** bacteria: *Klebsiella, Pseudomonas,* and *Serratia* spp.	Parenteral use; renal elimination	GI upsets, headache, vertigo; no cross-allergenicity with beta-lactams
Glycopeptides Vancomycin Teicoplanin	***Gram-positive*** activity includes MRSA and PRSP strains Teicoplanin as for vancomycin	Parenteral (oral for *C. difficile* colitis); renal elimination IV only, long half-life	***"Red man" syndrome,*** rare nephrotoxicity
Lipopeptide Daptomycin	***Gram-positive*** activity; used in endocarditis and sepsis	Renal elimination	Myopathy; monitor CPK weekly

All the drugs listed are bactericidal cell wall synthesis inhibitors except daptomycin, which destabilizes bacterial cell membranes.
CPK, creatine phosphokinase; MRSA, methicillin-resistant *Staphyloccus aureus;* PRSP, penicillin-resistant *Streptococcus pneumoniae;* UT, urinary tract.

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2.2.5 Bacitracin

Bacitracin is a cyclic peptide antibiotic with strong bactericidal action against gram-positive bacteria.

Mechanism of Action Bacitracin interferes with the assembly of the cell wall by preventing dephosphorylation of a carrier molecule for peptidoglycans.

Pharmacokinetics Bacitracin is poorly absorbed in the gastrointestinal tract and is predominantly used as a topical agent.

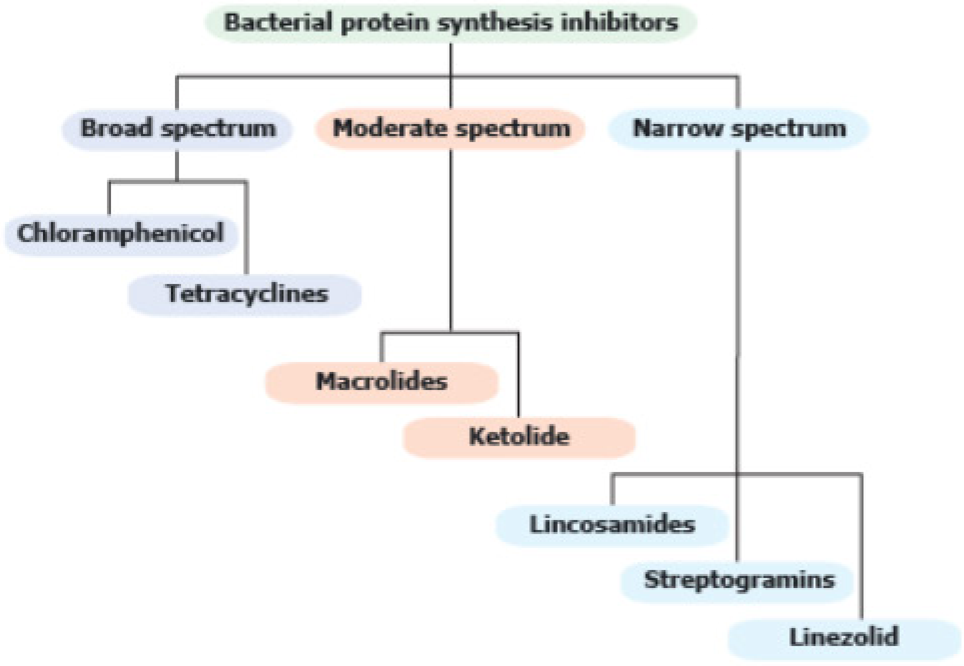
Resistance Mechanisms Bacitracin resistance is uncommon, but has been reported in some *Enterococcus* and *Streptococcus* species.

Spectrum of Activity Bacitracin has activity against *gram-positive* bacteria, particularly skin flora.

Adverse Effects Bacitracin can cause severe nephrotoxicity when given intravenously.

2.3 Protein Synthesis Inhibitors

As a class of antibacterials, these agents disrupt the ability of bacteria to synthesize protein. This *slows or stops the growth of bacteria,* making it easier for the host's immune system to defeat the infection. Protein synthesis inhibitors are generally *bacteriostatic,* although there are exceptions that have bactericidal effect, such as aminoglycosides.



▲**Figure 5-2.3** Protein Synthesis Inhibitors

2.3.1 Tetracyclines (Tetracycline, Doxycycline, Minocycline)

Tetracyclines are among the most prominent of the broad-spectrum agents that inhibit bacterial protein synthesis.

Mechanism of Action Tetracyclines bind to the bacterial 30S ribosomal subunit, leading to misreading during protein synthesis. Tetracyclines are generally *bacteriostatic*.

Pharmacokinetics Doxycycline and minocycline are absorbed well from the gastrointestinal tract regardless of food. Tetracycline and demeclocycline are absorbed much better on an empty stomach.

Resistance Mechanisms Enhanced efflux is the primary method of resistance, mediated by transporter pumps encoded by plasmids. A second mechanism of resistance is ribosome protection, caused by other proteins that interfere with tetracycline binding to the bacterial ribosome.

Memory Aid

"Buy at 30; CELL at 50"

- 30S is inhibited by Aminoglycosides and Tetracyclines.
- 50S is inhibited by **C**hloramphenicol, **E**rythromycin, **L**inezolid, and c**L**indamycin (which is a Lincosamide).

Spectrum of Activity Tetracyclines have a fairly wide spectrum of action against gram-positive and gram-negative organisms. The drugs are first-line therapy for chlamydia, including *C. psittaci*; rickettsiae (typhus, Rocky Mountain spotted fever); Ehrlichiosis, and brucellosis. They also are used to treat spirochete infections like syphilis and Lyme disease; *mycoplasma*; and *Propionibacterium* acnes such as rosacea. *Doxycycline* is currently the most commonly used of the tetracyclines and is first-line therapy for chlamydia and rickettsial infection.

Adverse Effects Tetracyclines, particularly tetracycline itself, can cause *photosensitivity* (increased risk of sunburn). The drug can also incorporate into teeth and bone, and may cause yellow-gray discoloration of teeth when used in children. Tetracycline is *not recommended for use in children, pregnant women* in second or third trimester, or in women who are breastfeeding. A very rare adverse effect of tetracyclines is the *Fanconi syndrome,* which is characterized by lack of renal reabsorption of glucose, amino acids, uric acid, phosphate, and bicarbonate.

2.3.2 Aminoglycosides (Gentamicin, Amikacin, Tobramycin, Streptomycin)

Aminoglycosides are antibiotics that are predominantly administered intravenously for serious gram-negative infections.

Mechanism of Action Aminoglycosides bind to the 30S subunit of bacterial ribosomes and cause *errors in translation*. Unlike most other antibacterials that target protein synthesis, aminoglycosides have bactericidal action.

Pharmacokinetics Aminoglycosides are given parenterally or topically due to poor absorption in the gastrointestinal tract.

Resistance Mechanisms Resistance to aminoglycosides is not common but can involve three mechanisms:

- Enzymatic degradation.
- Inability of drug to enter the bacterium.
- Alteration of the 30S subunit to prevent aminoglycoside binding.

Spectrum of Activity Aminoglycosides are predominantly active against *gram-negative* organisms, although they can be *used in conjunction with β-lactam antibiotics for severe gram-positive infections*. Aminoglycosides are active against most *Pseudomonas* strains.

- **Gentamicin:** The most commonly used of the aminoglycosides and has good activity against *Pseudomonas aeruginosa*.
- **Tobramycin:** Commonly used to treat gram-negative infections in patients with *cystic fibrosis*.
- **Streptomycin:** Has limited use due to resistance. It is a second-line agent for treatment of *Mycobacterium tuberculosis*.

Important Concept

The five main options for the treatment of *Pseudomonas aeruginosa are*:

- Ceftazidime or other anti-pseudomonal cephalosporin
- Aminoglycosides (especially tobramycin)
- Piperacillin/tazobactam
- Imipenem
- Ciprofloxacin

Adverse Effects The main adverse effects of aminoglycosides are *ototoxicity (cranial nerve VIII damage)* and *nephrotoxicity*. The risk of nephrotoxicity is increased when aminoglycosides are used concurrently with cephalosporins or other nephrotoxic medications. It is important to monitor aminoglycoside plasma levels and to avoid excessively high trough levels.

2.3.3 Chloramphenicol

Chloramphenicol is a broad-spectrum antibiotic that is uncommonly used in the United States because of adverse effects.

Mechanism of Action Chloramphenicol inhibits peptide bond formation by binding to bacterial 50S ribosomal subunit. Chloramphenicol is *bacteriostatic*.

Pharmacokinetics Chloramphenicol has excellent oral absorption and readily crosses the blood-brain and placental barriers. Chloramphenicol also may be given topically for ocular infections.

Resistance Mechanisms Bacteria gain resistance by a *plasmid-encoded enzyme (acetyltransferase)* that inactivates the drug.

Spectrum of Activity Chloramphenicol has broad-spectrum activity against gram-positive and gram-negative aerobes and anaerobes, as well as *Rickettsia.* Chloramphenicol is occasionally used for severe rickettsial infection or typhoid fever.

Adverse Effects The main adverse effect of chloramphenicol that limits its use is *aplastic anemia,* a rare, idiosyncratic response that can be fatal. Another adverse effect is seen when chloramphenicol is used in infants, who cannot efficiently metabolize and eliminate the drug. This can potentially lead to toxic concentrations and the *gray baby syndrome,* characterized by shock, abdominal distension, and cyanosis.

Important Concept

Chloramphenicol would likely *not* be an appropriate treatment choice on a Step 1 question.

2.3.4 Macrolides (Erythromycin, Azithromycin, Clarithromycin)

The macrolides are commonly used protein synthesis inhibitors with a broad spectrum of activity.

Mechanism of Action Macrolides inhibit the bacterial 50S ribosomal subunit and have predominantly *bacteriostatic* action.

Pharmacokinetics Macrolides have generally good oral absorption.

Resistance Mechanisms Resistance to macrolides is by three possible mechanisms:

- Increased efflux.
- Production of methylase enzyme that modifies and protects the ribosomes from macrolide binding.
- Production of hydrolyzing enzymes that destroy the macrolide.

Spectrum of Activity Macrolides have broad spectrum and are particularly useful for some *"atypical" organisms* such as *Mycoplasma*, *Chlamydia*, and *Legionella*.

- **Erythryomycin:** A common second-line drug to penicillin, it is active against *Mycoplasma, Chlamydia, Corynebacterium diphtheriae,* Lyme disease, *Listeria,* and *Bartonella*.

Memory Aid

Remember the long **O** in the names for macrolides: erythr**O**mycin, azithr**O**mycin, and clarithr**O**mycin

- **Azithromycin:** Has similar coverage to erythromycin but also is active against *Moraxella* and *Haemophilus influenzae* and is the *drug of choice* for *Legionella*. Azithromycin has convenient five-day dosing *("Z-Pak")* for upper respiratory tract infections and is available in a single-dose (1 g) treatment for chlamydia or chancroid.
- **Clarithromycin:** Has similar coverage to erythromycin but also covers *Mycobacterium leprae* and *Mycobacterium avium* complex. Clarithromycin can be used as part of "triple therapy," together with amoxicillin and omeprazole, to eradicate *Helicobacter pylori*.

Adverse Effects Macrolides have relatively minor adverse effects. Erythromycin can *inhibit cytochrome P450 enzymes* and can cause drug-drug interactions.

2.3.5 Clindamycin

Clindamycin is a lincosamide antibacterial structurally unrelated to macrolides.

Mechanism of Action Clindamycin has similar mechanism of action to macrolides, namely binding to the 50S ribosomal subunit.

Pharmacokinetics Clindamycin has good oral absorption.

Resistance Mechanisms Gram-negative aerobes are resistant to clindamycin due to lack of permeation of the drug through the outer membrane.

Spectrum of Activity Clindamycin has excellent coverage of gram-negative anaerobes, including *Bacteroides* and *Fusobacterium.*

Adverse Effects Clindamycin's major adverse side effect is as a trigger for pseudomembranous colitis (*Clostridium difficile* infection) by disruption of normal gut flora.

Important Concept

Clostridium difficile is the cause of pseudomembranous colitis. The treatment of choice is metronidazole. An alternative for those who cannot tolerate metronidazole is vancomycin in special oral formulation.

2.3.6 Linezolid

Linezolid is a synthetic oxazolidinone antibacterial effective against gram-positive cocci and rods.

Mechanism of Action Linezolid inhibits the 50S ribosomal subunit. Linezolid is generally classified as bacteriostatic, but is often bactericidal against *Streptococcus* species.

Pharmacokinetics Linezolid is effective by oral or intravenous administration.

Resistance Mechanisms Resistance occurs by mutation of the bacterial 50S binding site.

Spectrum of Activity Linezolid is predominantly used for treatment of infection caused by *gram-positive* cocci, particularly vancomycin-resistant *Enterococcus* and methicillin-resistant *Staphylococcus aureus.*

Adverse Effects Thrombocytopenia is the most common serious side effect in patients who take the drug for more than two weeks. Linezolid is also a weak *monoamine oxidase inhibitor (MAOI)*. Serotonin syndrome has been reported in patients taking both linezolid and selective serotonin reuptake inhibitors.

Important Concept

Vancomycin has traditionally been the agent of choice for *Enterococcus*. However, with increasing resistance to vancomycin (VRE), other options are sometimes required: linezolid, penicillin plus aminoglycoside, or quinupristin-dalfopristin.

2.3.7 Streptogramin (Quinupristin-Dalfopristin)

Quinupristin-dalfopristin are streptogramin antibiotics that are given together for serious infections due to gram-positive organisms.

Mechanism of Action Quinupristin and dalfopristin both inhibit the bacterial 50S ribosomal subunit.

Pharmacokinetics Quinupristin-dalfopristin are poorly absorbed orally and are given intravenously.

Resistance Mechanisms Resistance to quinupristin-dalfopristin is currently rare but has been detected in *Enterococcus.*

Spectrum of Activity Quinupristin-dalfopristin is effective against *gram-positive* organisms, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus (E. faecium,* not *E. faecalis)*

Adverse Effects Quinupristin-dalfopristin can cause myalgias and arthralgias. Quinupristin-dalfopristin also inhibits the cytochrome P450 3A4 isoform and can thus cause drug-drug interactions.

▼**Table 5–2.3** Protein Synthesis Inhibitors

Subclass	Mechanism of Action	Activity & Clinical Uses	Pharmacokinetics & Interactions	Toxicities
Tetracyclines Tetracycline Doxycycline Minocycline Tigecycline	Bind 30S ribosomal subunit; bacteriostatic; tigecycline has broadest spectrum and resistance is less common	Infections due to chlamydiae, mycoplasma, rickettsiae, spirochetes, and *H. pylori;* treatment of acne (low dose)	Oral, IV; renal and biliary clearance Doxycycline mainly gastrointestinal (GI) elimination and long half-life	GI upsets, deposition in developing bones and teeth, photosensitivity, superinfection
Macrolides Erythromycin Azithromycin Clarithromycin Telithromycin	Bind to 50S ribosomal subunit; bacteriostatic; least resistance to telithromycin	Community-acquired ***pneumonia, pertussis,*** corynebacteria, and chlamydial infections	Oral; IV for erythromycin, azithromycin Hepatic clearance, azithromycin long half-life (>40 hrs)	GI upsets, hepatic dysfunction; QT elongation; ***CYP450 inhibition*** (*not* azithromycin)
Lincosamide Clindamycin	Bind to 50S ribosomal subunit; bacteriostatic	Skin, ***soft tissue,*** and anerobic infections	Oral, IV; hepatic clearance	GI upsets; *C. difficile* colitis
Streptogramins Quinupristin-dalfopristin	Binds to 50S ribosomal subunit; bactericidal	Staphylococcal infections, vancomycin-resistant *E. faecium*	IV; renal clearance	Infusion-related arthralgia and myalgia; CYP450 inhibition
Chloramphenicol	Binds to 50S ribosomal subunit; bacteriostatic	Wide-spectrum, but mainly backup	Oral, IV; hepatic clearance, short half-life	Dose-related anemia; gray baby syndrome
Linezolid	Binds to 23S RNA of 50S subunit; bacteriostatic	Activity includes MRSA, PRSP, and VRE strains	Oral, IV; hepatic clearance	Dose-related anemia, neuropathy, optic neuritis; serotonin syndrome with SSRIs

MRSA, methicillin-resistant staphylococci; PRSP, penicillin-resistant pneumococci; SSRIs, selective serotonin reuptake inhibitators; VRE, vancomycin-resistant enterococci.

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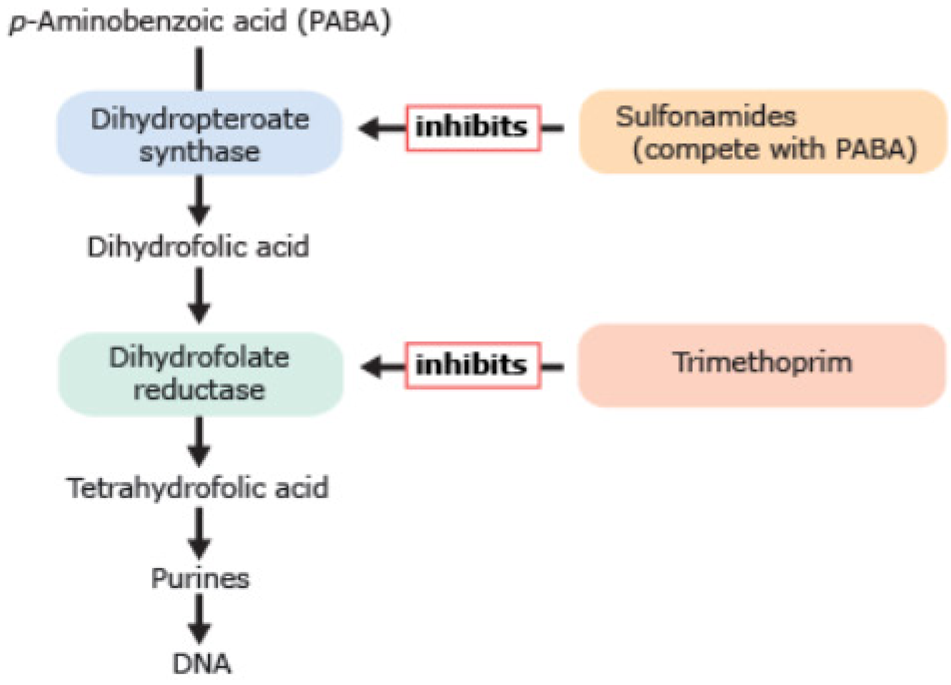
2.4 Folic Acid Synthesis Inhibitors

This class of antibacterial agents disrupts the synthesis of folic acid within bacteria, slowing or stopping their growth. These bacteriostatic agents typically have a broad spectrum of activity.

2.4.1 Sulfonamides

Sulfonamides are commonly used antibiotics. A combination of two antibiotics, *trimethoprim-sulfamethoxazole (TMP),* is the most widely used antibiotic in the United States.

Mechanism of Action Sulfonamides are *bacteriostatic* and act by *blocking folic acid synthesis*. Sulfonamides inhibit the enzyme dihydropteroate synthase, which converts PABA to dihydrofolic acid. Trimethoprim blocks a different step in the same pathway by inhibiting dihydrofolate reductase.



▲ **Figure 5-2.4** Action of Folic Acid Synthesis Inhibitors

Pharmacokinetics Sulfonamides displace bilirubin from protein binding sites and are not recommended in neonates due to risk of kernicterus.

Resistance Mechanisms Sulfonamides are rarely given as single agents due to resistance. Bacteria resistance may be due to overproduction of PABA, mutation of dihydropteroate synthase, or reduced permeability. Bacterial resistance to TMP is so far relatively rare due to this combination product inhibiting two separate steps in the bacterial folic acid pathway.

Important Concept

Avoid choosing trimethoprim alone as an answer on Step 1 questions. Use as only one component of combination therapy.

Spectrum of Activity TMP is relatively broad-spectrum, with activity against *Staphylococcus, Streptococcus, Haemophilus influenzae, E. coli, Proteus, Klebsiella, Shigella, Salmonella,* and *Pneumocystis jiroveci.* Topical sulfonamides such as silver sulfadiazine are commonly used for prevention of burn wound infections. TMP is the first-line drug for *Pneumocystis* treatment or prophylaxis and for uncomplicated urinary tract infections.

▼**Table 5–2.4** Folic Acid Synthesis Inhibitors

Subclass	Mechanism of Action	Activity & Clinical Uses	Pharmacokinetics & Interactions	Toxicities
Trimethoprim-sulfamethoxazole	Synergistic inhibition of folic acid synthesis; the combination is bactericidal—"sequential blockade"	Urinary tract, respiratory, ear, and sinus infections; *P. jiroveci* pneumonia; toxoplasmosis; nocardiosis	Oral, IV; renal clearance, half-life ~8 hrs	Rash, fever, bone marrow suppression, hyperkalemia; high incidence of adverse effects in AIDS
Other folate antagonists Sulfisoxazole Sulfadiazine (+/− pyrimethamine) Trimethoprim Pyrimethamine (+/− sulfadoxine)	Sulfonamides inhibit dihydropteroate synthase Trimethoprim and pyrimethamine inhibit dihydrofolate reductase	Simple urinary tract infections (oral) and topical in burn or eye infections (sulfonamides); toxoplasmosis (sulfadiazine + pyrimethamine); malaria (sulfadoxine + pyrimethamine)	Hepatic and renal clearance and extensive plasma protein binding of sulfonamides (displace bilirubin, methotrexate, and warfarin)	Common—oral doses of sulfonamides cause GI upsets, acute hemolysis in G6PDH deficiency, possible ***crystalluria*** and rash (assume cross-hypersensitivity)

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Adverse Effects Allergic reactions are common with sulfonamides, including rare, serious reactions such as *Stevens-Johnson syndrome* or toxic epidermal necrolysis. Sulfonamides can precipitate *hemolytic anemia in glucose-6-phosphate dehydrogenase (G6PD)-deficient patient*. Long-term use of TMP can cause megaloblastic anemia due to trimethoprim inhibition of host cell dihydrofolate reductase.

2.5 Nucleic Acid Disruptors

This class of bactericidal agents kills bacteria by targeting the enzymes that regulate DNA structure and function.

2.5.1 Nitrofurantoin

Nitrofurantoin is an older antibiotic that is used to treat *urinary tract infections*.

Mechanism of Action Nitrofurantoin is converted inside the bacteria to a toxic metabolite.

Pharmacokinetics Nitrofurantoin is concentrated in the urine by filtration and secretion.

Resistance Mechanisms Resistance is rare with nitrofurantoin.

Spectrum of Activity Nitrofurantoin is active against gram-positives and *gram-negatives,* including most common pathogens such as *E. coli* that are involved in urinary tract infections. Nitrofurantoin is a second-line agent for urinary tract infections.

Adverse Effects Nitrofurantoin can precipitate *hemolytic anemia* in a glucose-6-phosphate dehydrogenase (G6PD)-deficient patient.

2.5.2 Fluoroquinolones (Ciprofloxacin, Levofloxacin, Gatifloxacin, Moxifloxacin)

Fluoroquinolones are widely used bactericidal antibiotics, primarily for urinary and respiratory tract infections.

Mechanism of Action Fluoroquinolones inhibit bacterial DNA gyrase (topoisomerase III).

Pharmacokinetics Fluoroquinolones are generally absorbed well orally. Most also are available in intravenous formulations.

Resistance Mechanisms Resistance to fluoroquinolones has unfortunately been increasing steadily throughout the last decade. The three main mechanisms are mutations in the DNA gyrase, decreased permeability, and increased efflux.

Spectrum of Activity Fluoroquinolones are *broad-spectrum,* particularly for aerobic organisms. Quinolones are commonly used for urinary tract infections, community acquired pneumonia, *otitis externa,* and pulmonary infections in cystic fibrosis.

Adverse Effects The most serious effect of fluoroquinolones is *damage to cartilage*. Fluoroquinolones have been associated with tendonitis and tendon rupture. They are *not recommended in pregnancy* and also are relatively *contraindicated in children* due to risk of damaging developing cartilage.

Memory Aid

All fluoroquinolones have "flox" in their names: cipro**flox**acin, levo**flox**acin, gati**flox**acin, and moxi**flox**acin.

▼Table 5–2.5 Nucleic Acid Disruptors

Subclass	Mechanism of Action	Activity & Clinical Uses	Pharmacokinetics & Interactions	Toxicities
Ciprofloxacin	Inhibits DNA replication via binding to DNA gyrase (gram-negative organisms) and topoisomerase IV (gram-positive organisms); bactericidal resistance: see fluoroquinolones below	Effective in urogenital, GI tracts, and some respiratory infections; activity versus gonococci rapidly declining; limited use in tuberculosis	Oral, IV; mostly renal clearance, half-life 4 hrs Oral absorption impaired by cations	GI upsets, CNS effects (dizziness, headache); tendinitis due to effects on cartilage (try to ***avoid in young children and pregnancy***)
Other fluoroquinolones Norfloxacin Ofloxacin Levofloxacin Moxifloxacin Gemifloxacin	Mechanism identical to that of ciprofloxacin; bactericidal resistance via changes in target enzymes (e.g., ***DNA gyrase***) and possibly formation of inactivating enzymes	Norfloxacin and ofloxacin used mainly for urinary tract infections; levofloxacin and moxifloxacin are "respiratory" fluoroquinolones with enhanced activity against gram-positive cocci and atypicals (chlamydia, mycoplasma)	Oral and IV forms of levofloxacin and moxifloxacin; mostly renal clearance (not moxifloxacin—hepatic) Long half-lives of gemifloxacin and moxifloxacin permit once-daily dosing	Like ciprofloxacin (see above) QT prolongation (levofloxacin, gemifloxacin, and moxifloxacin) Caution with use of class 1A and III antiarrhythmics

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2.5.3 Metronidazole and Tinidazole

Metronidazole and tinidazole are two members of the nitromidazole family of antibacterials. They are used mainly to treat infections caused by anaerobic bacteria and protozoa.

Mechanism of Action The nitro group of metronidazole and tinidazole is reduced inside bacteria and protozoa, forming a toxic by-product.

Pharmacokinetics Metronidazole and tinidazole can be given either orally or intravenously.

Resistance Mechanisms Resistance is rare to metronidazole and tinidazole, although decreased susceptibility to *Bacteroides* has been reported.

Spectrum of Activity Metronidazole and tinidazole have predominant activity against anaerobic bacteria (*Bacteroides, Clostridium*), protozoa (*Trichomonas, Gardnerella, Giardia*), and *Helicobacter pylori.*

Adverse Effects Metronidazole has an unpleasant, metallic taste. It also can cause a disulfiram-like reaction by inhibition of aldehyde reductase.

2.5.4 Rifamycins (Rifampin, Rifabutin, Rifapentine)

The rifamycins are a group of structurally similar macrocyclic antibiotics. They are primarily used to treat tuberculosis—see mycobacteria below—and have additional clinical uses, including prophylaxis against *N. meningococcus* and *H. influenza* meningitis.

Mechanism of Action Rifamycins are bactericidal and act by blocking transcription through the β-subunit of *bacterial DNA-dependent RNA polymerase*.

Pharmacokinetics Rifampin is a classic inducer of cytochrome P450 enzymes and can decrease concentrations of other drugs, such as cyclosporine, carbamazepine, and oral contraceptives, that are metabolized by CYP enzymes.

Resistance Mechanisms Resistance to rifamycins is via mutations in the bacterial RNA polymerase.

Spectrum of Activity Rifampin has antibacterial activity against *Mycobacterium tuberculosis*, *N. meningitidis*, and *H. influenza*. Rifampin is also used in combination therapy for severe staphylococcal infections associated with catheters and prosthetics.

Adverse Effects Rifampin is associated with hepatitis and cholestatic jaundice. Rifampin is also associated with a "flu-like" syndrome in which the patient experiences general malaise. A striking side effect of rifampin is *red-orange discoloration* of body secretions such as urine, sweat, and tears. This is harmless but can alarm patients who are not warned.

2.6 Cell Membrane Disruptors

There are two antibacterials (polymyxin and triclosan) that act by disrupting the bacterial cell membrane. These drugs are predominantly used in topical forms.

2.6.1 Polymyxins

Polymyxins are compounds with a cyclic peptide and long hydrophobic tail. Polymyxin B is used clinically and has bactericidal action against *gram-negative* bacteria by acting as a *detergent* against the cell membrane. Polymyxins cannot penetrate the cell wall of gram-positive bacteria. Polymyxin B is used in a variety of topical (such as Neosporin) and ophthalmic formulations. In rare circumstances, polymyxin B can be administered intravenously for serious gram-negative infections or intrathecally for gram-negative meningitis. Parenteral administration carries a risk of *nephrotoxicity*.

2.6.2 Triclosan

Triclosan has antibacterial and antifungal action by inhibiting fatty acid synthesis. This disrupts cell membrane synthesis and repair. The drug is heavily used in *antibacterial soaps, detergents,* toothpastes, and cleaning supplies. Treatment of skin with triclosan can be an effective means of decolonizing methicillin-resistant *Staphylococcus aureus* (MRSA) from the skin. There are concerns about bacterial resistance to triclosan due to its widespread use.

▼Table 5–2.6 Summary of Antibacterial Therapies

Pathogen	Drug(s) of First Class	Alternative Drugs
***Enterococcus* spp.**	Ampicillin +/− gentamicin	Vancomycin +/− gentamicin
S. aureus or epidermis Methicillin-susceptible	Nafcillin	Cephalosporin, clindamycin, fluoroquinolone, imipenem
Methicillin-resistant	Vancomycin +/− gentamicin +/− rifampin	Daptomycin, doxycycline, fluoroquinolone, linezolid, streptogramins
S. pneumoniae		
Penicillin-susceptible	Penicillin G, amoxicillin	Cephalosporin, clindamycin, fluoroquinolone, macrolide, TMP-SMZ
Penicillin-resistant	Vancomycin + ceftriaxone or cefotaxime +/− rifampin	Linezolid, streptogramins, third-generation fluoroquinolone
N. gonorrhoeae	Ceftriaxone, cefixime	Spectinomycin, azithromycin
N. meningitidis	Third-generation cephalosporin	Penicillin G, cholamphenicol
M. catarrhalis	Cefuroxime, TMP-SMZ	Amoxicillin-clavulanate, third-generation fluoroquinolone, macrolide
C. difficile	Metronidazole	Vancomycin, bacitracin
C. trachomatis	Macrolide or tetracycline	Clindamycin, ofloxacin
C. pneumoniae	Macrolide or tetracycline	Fluoroquinolone
M. pneumoniae	Macrolide or tetracycline	Fluoroquinolone
T. pallidum	Penicillin G	Doxycycline, ceftriaxone, azithomycin

Based on treatment guidelines (USA) available in January 2009

(continued on next page)

▼Table 5–2.6 Summary of Antibacterial Therapies *(continued)*

Pathogen	Drug(s) of First Class	Alternative Drugs
Bacteroides	Metronidazole	Carbapenems, penicillins + beta-lactamase inhibitor, chloramphenicol
Campylobacter jejuni	Macrolide	Fluoroquinolone, tetracycline
***Enterobacter* spp.**	Carbapenem, TMP-SMZ	Aminoglycoside, cefepime, fluoroquinolone, third-generation cephalosporin
E. coli	Cephalosporin (first- and second-generation), TMP-SMZ	Many penicillins +/− beta-lactamase inhibitor, fluoroquinolones, aminoglycosides
G. vaginalis	Metronidazole	Clindamycin
K. pneumoniae	Cephalosporin (first- or second-generation), TMP-SMZ	Carbapenems, penicillins + beta-lactamase inhibitor, aminoglycosides, fluoroquinolones
P. mirabilis	Ampicillin	Cephalosporins, penicillins + beta-lactamase inhibitor, aminoglycosides, TMP-SMZ, fluoroquinolones
Proteus-indole positive	Cephalosporin (first- or second-generation), TMP-SMZ	Carbapenems, penicillins + beta-lactamase inhibitor, aminoglycosides, fluoroquinolones
S. typhi	Ceftriaxone or fluoroquinolone	Chloramphenicol, TMP-SMZ, ampicillin
***Serratia* spp.**	Carbapenem	Aminoglycoside, third-generation cephalosporin, fluoroquinolone, TMP-SMZ
***Shigella* spp.**	Fluoroquinolone	Azithromycin, TMP-SMZ, ampicillin, ceftriaxone

Based on treatment guidelines (USA) available in January 2009

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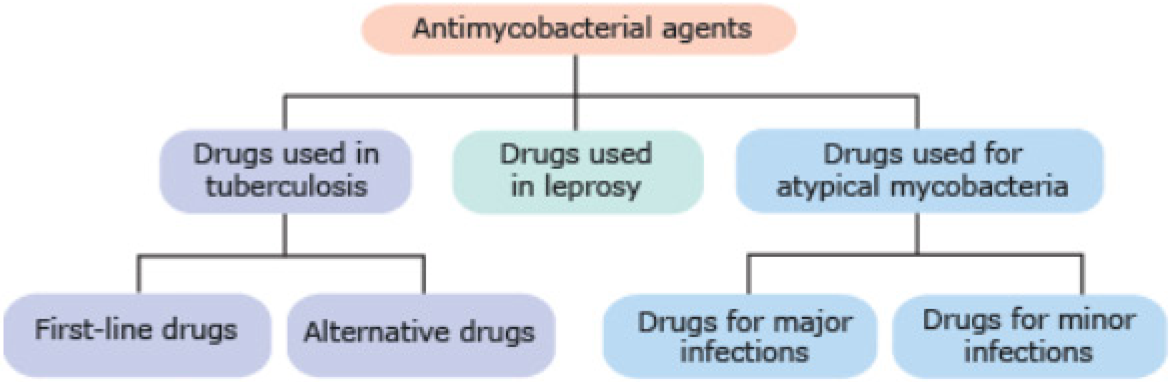
3 Antimycobacterial Drugs

Mycobacteria are bacteria that resemble fungus in the way they grow—hence the prefix *myco.* These microorganisms are responsible for tuberculosis and leprosy, among other diseases. A fairly limited set of drugs is used to treat mycobacterial infections.


Antimycobacterial agents
Drugs used in tuberculosis
Drugs used in leprosy
Drugs used for atypical mycobacteria
First-line drugs
Alternative drugs
Drugs for major infections
Drugs for minor infections

▲ **Figure 5-3.0** Antimycobacterial Agents

3.1 Treatment for Tuberculosis

Tuberculosis can be difficult to treat. On exposure to *Mycobacterium tuberculosis,* individuals may develop primary infection. This can progress to active disease or become latent. *Latent tuberculosis* may reactivate later, with a higher risk of reactivation in immunocompromised patients, as with HIV infection. Combination drug therapy is often required, especially for multidrug-resistant strains. Drug selection is guided by drug resistance testing:

- Primary drugs for treating tuberculosis are *isoniazid, rifampin, pyrazinamide,* and *ethambutol*.
- Secondary drugs for tuberculosis are streptomycin, cycloserine, and fluoroquinolones. These are generally used for drug-resistant strains or for patients who can tolerate one or more of the primary drugs.

3.2 Isoniazid

Isoniazid (isonicotine hydrazine, INH) is a bactericidal drug that is the most common medication used for treating tuberculosis.

Mechanism of Action Isoniazid is a *prodrug* that is activated by catalase-peroxidase *(KatG)* in the mycobacterium. The metabolite inhibits mycolic acid synthesis and thereby interferes with mycobacterial cell wall formation. The activated drug covalently binds to and inhibits mycobacterial enoyl-acyl carrier protein reductase *(InhA)* and β-ketoacyl-ACP synthase (KasA).

Pharmacokinetics Isoniazid is well absorbed orally and penetrates caseous lesions well. Isoniazid is primarily excreted renally and should be used with caution in renal failure patients.

Resistance Mechanisms Resistance to isoniazid is primarily due to mutations in InhA or KasA or to overexpression of these enzymes.

Spectrum of Activity Isoniazid is a narrow-spectrum antibiotic that has activity predominantly against mycobacteria.

Adverse Effects The two main adverse effects of isoniazid are *hepatitis* and *peripheral neuropathy*. Hepatitis is caused by a toxic metabolite (monoacetylhydralazine). Physicians often monitor liver enzymes such as alanine aminotransferase in patients receiving isoniazid. Peripheral neuropathy can be prevented by prophylaxis with *vitamin B6 (pyridoxine)*.

3.3 Rifamycins (Rifampin, Rifabutin, Rifapentine)

The rifamycins, macrocyclic antibiotics discussed above, often are used to treat tuberculosis. These agents should not be used as monotherapy for tuberculosis due to risk of resistance.

3.4 Pyrazinamide

Pyrazinamide is a relative of nicotinamide. Although less commonly used than rifampin or isoniazid, pyrazinamide is one of the primary drugs for treating tuberculosis.

Mechanism of Action Pyrazinamide is converted by mycobacterial enzymes to a toxic metabolite that kills bacteria at low pH in lysosomes.

Pharmacokinetics Pyrazinamide is well absorbed orally and eliminated by both hepatic metabolism and renal clearance. Pyrazinamide crosses the meninges well and is a primary treatment for tuberculous meningitis.

Resistance Mechanisms Resistance to pyrazinamide can occur by lack of uptake and mutations in the enzyme that converts pyrazinamide to the toxic metabolite.

Spectrum of Activity Pyrazinamide is used almost solely for the treatment of tuberculosis.

Adverse Effects Adverse effects of pyrazinamide include myalgia, hepatitis, and gout (hyperuricemia).

3.5 Ethambutol

Ethambutol is an antibiotic that is only active against mycobacteria.

Mechanism of Action Ethambutol inhibits arabinosyltransferase, an enzyme required in the synthesis of mycobacterial cell wall. Ethambutol is bacteriostatic, but can be bacteriocidal at higher doses.

Pharmacokinetics Ethambutol is well absorbed orally.

Resistance Mechanisms Ethambutol resistance is generally conferred by mutation or overexpression of arabinosyltransferase.

Spectrum of Activity Ethambutol is used exclusively to treat tuberculosis.

Adverse Effects The classic adverse effect of ethambutol is optic neuritis with red/green color blindness and blurry vision. Ethambutol therapy is not recommended for children.

3.6 Streptomycin

Streptomycin is an aminoglycoside that is a second-line drug for treating tuberculosis.

Mechanism of Action Like other aminoglycosides, streptomycin inhibits protein synthesis by inhibition of the bacterial 30S ribosomal subunit.

Pharmacokinetics Streptomycin is generally administered intramuscularly due to poor oral absorption.

▼**Table 5–3.6** Antimycobacterial Agents[1]

Drugs	Mechanism of Action	Activity & Clinical Uses	Pharmacokinetics & Interactions	Toxicities
Isoniazid (INH)	***Requires bioactivation;*** inhibits mycolic acid synthesis; resistance via expression of *katG* and *inhA* genes	Bactericidal; primary drug for LTBI and a primary drug for use in combinations	Oral, IV forms; hepatic clearance (fast and slow acetylators); inhibits metabolism of carbamazepine, phenytoin, and warfarin	Hepatotoxicity, peripheral neuropathy (use pyridoxine); hemolysis in G6PDH deficiency
Rifamycins Rifampin (RIF)[2] Rifabutin Rifapentine	***Inhibit DNA-dependent RNA polymerase;*** resistance emerges rapidly when drug is used alone	Bactericidal; RIF is an optional drug for LTBI, a primary drug used in combinations for active TB	Rifampin (oral, IV); others oral; enterohepatic cycling with some metabolism; induced formation of CYP450 by RIF leads to decreased efficacy of many drugs (rifabutin less)	Rash, nephritis, cholestasis, thrombocytopenia; flu-like syndrome with intermittent dosing
Ethambutol (ETB)	***Inhibits formation of arabinoglycan,*** a component of mycobacterial cell wall; resistance emerges rapidly if drug is used alone	Bacteriostatic component of many drug combination regimens for active TB	Oral; renal elimination with large fraction unchanged; reduce dose in renal dysfunction	Dose-dependent visual disturbances, reversible on discontinuance; headache, confusion, hyperuricemia, and peripheral neuritis
Pyrazinamide (PYR)	Uncertain, but ***requires bioactivation*** via hydrolytic enzymes to form pyrazoic acid (active)	Bacteriostatic; component of many drug combination regimens for active TB	Oral; both hepatic and renal elimination (reduce dose in dysfunction)	Polyarthralgia (40% incidence), hyperuricemia, myalgia, maculopapular rash, porphyria, and photosensitivity; avoid in pregnancy
Streptomycin (SM)	Binds to 30S ribosomal subunit inhibiting protein synthesis	Bactericidal; used in TB when injectable drug needed, or in treatment of drug-resistant strains	Parenteral; renal elimination	Ototoxicity, nephrotoxicity

[1] Backup drugs include amikacin, aminosalicylic acid, ciprofloxacin, cycloserine, ethionamide, and levofloxacin.
[2] Rifampin is also used for eradication of staphylococci and meningococci in carriers.
G6PDH, glucose-6-phosphate dehydrogenase; LTBI, latent tuberculosis infection.

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Resistance Mechanisms Resistance to streptomycin can involve three mechanisms:

- Enzymatic degradation.
- Inability of drug to enter the bacterium.
- Alteration of the 30S subunit to prevent aminoglycoside binding.

Spectrum of Activity Streptomycin is also active against *Mycobacterium avium-intracellulare* and *M. kansasii*.

Adverse Effects Streptomycin shares the adverse effects of *ototoxicity* and *nephrotoxicity* with other aminoglycosides.

3.7 Other Antitubercular Drugs

For drug-resistant tuberculosis, occasionally additional antitubercular drugs need to be employed.

3.7.1 Cycloserine

Cycloserine inhibits mycobacterial cell wall synthesis by blocking peptide formation. Central nervous system side effects are common, including seizures.

3.7.2 Capreomycin

Capreomycin inhibits RNA synthesis and has similar adverse effects to aminoglycosides.

3.8 Tuberculosis Regimens

Step 1 questions occasionally ask about specific regimens for managing tuberculosis, either as prophylaxis or treatment of active infection.

3.8.1 Prophylaxis Regimens

Prophylaxis regimens are used for high-risk patients , such as the immunocompromised, very young or very old, or patients with recent PPD (skin test) conversion. The most common prophylaxis regimen is *isoniazid for six months*.

3.8.2 Treatment of Active Tuberculosis

For patients with known tuberculosis infection (from culture or sputum stain), the CDC recommends an initial *four-drug regimen* with isoniazid, rifampin, pyrazindamide, and ethambutol until sensitivity of the strain is known. Determination of sensitivity requires a culture of the organism and subsequent antibiotic testing, which can take several weeks or more. After sensitivity is known, treatment must include at least two drugs to which the tuberculosis strain is sensitive to in vitro. Common regimens are:

- Isoniazid + rifampin + pyrazinamide for six months.
- Isoniazid + rifampin for nine months.

3.8.3 Treatment of Tuberculosis During Pregnancy

The multidrug regimen of isoniazid, rifampin, and ethambutol is considered safe during pregnancy.

3.9 Treatment of Atypical Mycobacteria

Atypical mycobacterial infections are more common in immunocompromised individuals. The drugs used to treat these infections differ somewhat from the treatment of tuberculosis.

3.9.1 Mycobacterium Avium-Intracellulare (MAI) Complex

Infection with MAI can cause *pulmonary* or systemic disease. The standard treatment of *Mycobacterium avium-intracellulare* is *azithromycin* or *clarithromycin plus ethambutol*. If needed, rifampin, rifabutin, or ciprofloxacin can be added.

3.9.2 Leprosy

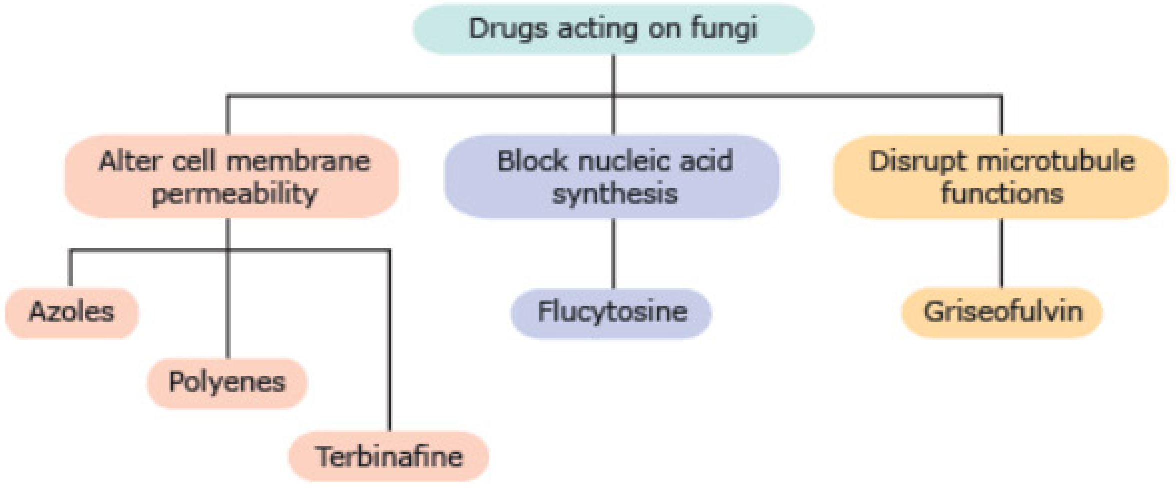
Leprosy is caused by *Mycobacterium leprae*. The World Health Organization recommends *triple regimen* of dapsone, clofazimine, and rifampin for 6 to 24 months. Dapsone is related to the sulfonamides and can cause erythema nodosum leprosum (painful skin lesions) as well as hemolytic anemia in patients with G6PD deficiency. Clofazimine can cause a *red-brown discoloration* of the skin. Eosinophilic enteritis has also been reported as an adverse effect.

Important Concept

Mycoplasma is one cause of "atypical pneumonia." The infection is not difficult to treat, but does require appropriate antibiotic selection. *Mycoplasma pneumonia* is readily treated by macrolides, such as azithromycin, and tetracyclines. Another option is moxifloxacin.

4 Antifungal Drugs

Fungal infection, or *mycosis*, is common in humans. Most infections represent superficial diseases of the skin and orifices. More serious infections typically develop only in *immunocompromised* patients. The set of drugs used to treat fungal infections is mostly distinct from the drugs used to treat infections caused by other microorganisms. Antifungal agents that most commonly appear in Step 1 questions are amphotericin, azoles, and caspofungin.


Drugs acting on fungi
Alter cell membrane permeability
Block nucleic acid synthesis
Disrupt microtubule functions
Azoles
Polyenes
Terbinafine
Flucytosine
Griseofulvin

▲**Figure 5-4.0** Antifungal Drugs

4.1 Overview of Fungal Infections

Fungal infections range from nuisances to life-threatening infections. Superficial infections include those affecting the skin, such as ringworm. Systemic fungal infections can be serious and difficult to treat, depending on the organism involved. Some invasive fungal infections, such as mucormycosis, require immediate surgical intervention.

4.1.1 Candida

Candida is a yeast and the most common organism involved in fungal infections. *Candida* infections can be relatively simple to treat, such as vaginal candidiasis ("yeast organism") or oral thrush. Systemic candidiasis usually occurs in immunocompromised individuals. The most common species of *Candida* is *Candida albicans*. An emerging organism is *Candida glabrata*, a species that is resistant to common antifungal agents.

4.1.2 Aspergillus

Aspergillus is a genus of molds, several of which (*A. fumigatus*, *A. flavus*) can cause human infection. Invasive *Aspergillus* infections are quite difficult to treat and represent a significant cause of mortality in immunocompromised patients, as in bone marrow transplant recipients.

4.1.3 Cryptococcus

Cryptococcus neoformans is a yeast that can cause infections, mainly in immunocompromised individuals. *Cryptococcus* can cause *pneumonia* and *meningitis*.

4.1.4 Histoplasma

Histoplasma capsulatum is a dimorphic fungus common throughout much of the central part of the United States. Many individuals are infected with *Histoplasma* and show no serious symptoms. A small number of patients experience systemic symptoms.

4.2 Amphotericin B

Amphotericin B is the prototype antifungal drug with a wide spectrum of activity, but it also can produce severe side effects.

Mechanism of Action Amphotericin interferes with ergosterol in the fungal cell membrane. Amphotericin causes artificial pores to develop, disrupting the integrity of the fungal membrane.

Pharmacokinetics Amphotericin is given orally to treat superficial infections (e.g., oral thrush) and intravenously to treat more serious infections. Amphotericin has a large volume of distribution and stays in tissues for months to a year.

Resistance Mechanisms Resistant fungi have low ergosterol content in their cell membranes.

Spectrum of Activity Amphotericin has a wide fungicidal spectrum of activity and is used for treatment of *severe infections* caused by *Aspergillus*, *Candida* (sometimes together with flucytosine), *Cryptococcus*, *Histoplasma*, *Mucor*, and *Sporothrix*.

Adverse Effects The most limiting aspect of amphotericin lies in the adverse effects that gave rise to the drug's nickname, *"Amphoterrible."* Amphotericin infusions can generate a variety of unpleasant acute effects, including fever, chills, muscle rigor, and hypotension (due to histamine release). These acute symptoms can be limited to some degree by slow infusion and prophylaxis with NSAIDs, antihistamines, and corticosteroids. More extended use of amphotericin (greater than 3–4 grams total over a lifetime) is associated with permanent renal tubule damage. Lipid formulations of amphotericin such as Ambisome are designed to improve efficiency and reduce toxicity, but are much more expensive.

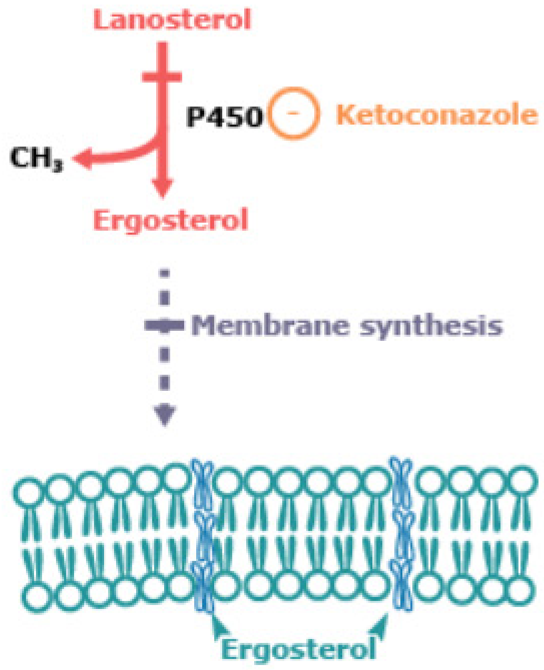
Important Concept

Extended use of amphotericin is asociated wth renal tube damage.

4.3 Azoles (Fluconazole, Itraconazole, Voriconazole)

Azoles are widely used fungicidal drugs. Ketoconazole is the prototype azole, but is rarely used clinically in the United States.

Mechanism of Action Azoles impair biosynthesis of ergosterol by inhibiting the fungal cytochrome P450 enzyme involved in conversion of lanosterol to ergosterol.



▲**Figure 5-4.3** Ergosterol Synthesis Blocked by Ketoconazole

Pharmacokinetics The azoles in general have good oral absorption. Azoles inhibit human cytochrome P450 enzymes, as they do in fungi, and are prone to cause drug-drug interactions such as inhibiting the metabolism of cyclosporine. Azoles also inhibit breakdown of estrogens, potentially leading to gynecomastia in males. Azoles are absorbed better at acidic pH; therefore, their absorption is reduced by acid-reducing drugs such as antacids, proton-pump inhibitors, and histamine-2 blockers.

Resistance Mechanisms Resistance to azoles is caused by *mutations in the fungal cytochrome P450 (C-14 α-demethylase)* responsible for synthesis of ergosterol.

Spectrum of Activity Azoles have a wide fungicidal spectrum of activity and are used for treatment of infections caused by *Candida*, *Cryptococcus* (azoles are the drug of choice for cryptococcal meningitis), *Blastomyces*, *Histoplasma*, *Coccidioides*, and ringworm fungi (dermatophytes).

Adverse Effects Other than the drug-drug and drug-hormone interactions mentioned above, azoles are also teratogenic and not recommended for use in pregnancy.

4.3.1 Fluconazole

Fluconazole is a widely used azole that has limited inhibition of cytochrome P450 enzymes. Fluconazole penetrates CSF well and is the *drug of choice for cryptococcal meningitis*. Fluconazole is effective against all forms of candidiasis. Fluconazole is not effective against *Aspergillus*. Resistance to fluconazole has led to increasing use of voriconazole.

4.3.2 Itraconazole

Itraconazole is well absorbed orally but *requires stomach acid for optimal absorption*. In contrast to fluconazole, itraconazole has poor CSF penetration and is not used for fungal meningitis. Itraconazole is the azole of choice for *AIDS-associated histoplasmosis*. Itraconazole inhibits cytochrome P450 activity and can thus cause drug-drug interactions.

4.3.3 Voriconazole

Voriconazole has a similar spectrum of action as itraconazole. Voriconazole is the *drug of choice for invasive aspergillosis,* with a much better side effect profile than amphotericin. Visual disturbances, a rare side effect, are usually reversible.

4.4 Flucytosine

Flucytosine is a seldom-used antifungal generally *restricted for serious infections*.

Mechanism of Action Flucytosine is activated by fungal cytosine deaminase to 5-fluorouracil (5-FU). 5-FU, which also is used as a chemotherapy agent for cancer, is an *antimetabolite* that disrupts RNA synthesis.

Pharmacokinetics Flucytosine is given intravenously due to poor oral absorption.

Resistance Mechanisms Some strains of *Candida* (*C. dubliniensis*) are resistant to flucytosine by not converting flucytosine to 5-FU.

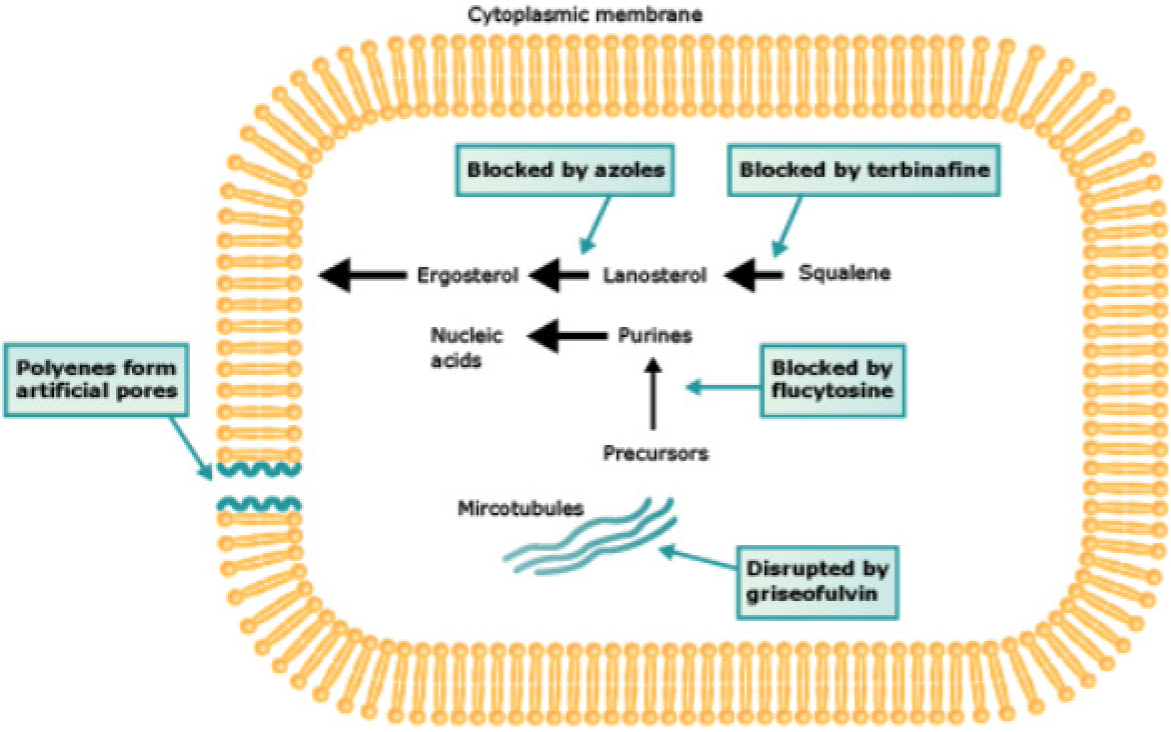
Spectrum of Activity Flucytosine is used mainly in combination with amphotericin B for severe candidal and cryptococcal infections.

Adverse Effects The major adverse effect is *bone marrow toxicity,* potentially leading to neutropenia and thrombocytopenia.

4.5 Echinocandins (Caspofungin, Micafungin, Anidulafungin)

Echinocandins are a new class of antifungals used mainly for invasive *Candida* and *Aspergillus* infections.

Mechanism of Action Echinocandins interfere with fungal cell wall synthesis by *inhibiting β-glucan synthase*.


Cytoplasmic membrane
Blocked by azoles
Blocked by terbinafine
Ergosterol
Lanosterol
Squalene
Nucleic acids
Purines
Polyenes form artificial pores
Blocked by flucytosine
Precursors
Mircotubules
Disrupted by griseofulvin

▶ **Figure 5-4.5** Sites of Antifungal Drug Action

Pharmacokinetics Echinocandins are given intravenously due to poor oral absorption.

Resistance Mechanisms Resistance is rare but has been described in *Candida* species due to mutations in the β-glucan synthase enzyme.

Spectrum of Activity Echinocandins are active against *Candida* and *Aspergillus,* but have poor activity against *Cryptococcus* or *Mucor*.

Adverse Effects Echinocandins are generally well tolerated, but have been noted to cause liver enzyme elevations.

4.6 Treatment of *Pneumocystis jiroveci*

Pneumocystis jiroveci (formerly *P. carinii*) was thought to be a parasite, but is now classified as an *unusual fungus that lacks ergosterol in its cell membranes,* thus precluding the use of amphotericin or azoles.

4.6.1 Pneumocystis Infections

Pneumocystis predominantly causes opportunistic infections in AIDS patients and other immunocompromised individuals.

4.6.2 Treatment Regimens

Trimethoprim-sulfamethoxazole is the treatment of choice as both prophylaxis and for active infection. Prophylactic therapy is usually started when CD4 count is below 200/mm^3. Backup drugs to trimethoprim-sulfamethoxazole are *pentamidine* and *atovaquone*.

4.7 Treatment of Superficial Mycotic Infections

Many of the drugs for treating superficial mycotic infections are available over the counter.

4.7.1 Terbinafine

Terbinafine can be given orally (requires prescription) or topically. The drug *inhibits fungal squalene epoxidase,* blocking ergosterol synthesis. Treatment of deep nail infections requires several months of therapy. Terbinafine can cause hepatotoxicity and neutropenia, and is also not recommended for nursing mothers due to accumulation in breast milk.

4.7.2 Griseofulvin

Griseofulvin is an older antifungal medication used for treatment of dermatophytes. Griseofulvin interferes with fungal mitosis. It has largely been replaced by terbinafine due to adverse effects, notably a disulfiram-like reaction with ethanol (inhibition of aldehyde dehydrogenase) and hepatitis.

4.7.3 Miconazole and Clotrimazole

Miconazole and clotrimazole are widely used topical azoles for treatment of dermatophytes ("athlete's foot," "jock itch").

4.7.4 Nystatin

Nystatin is a topical polyene antifungal with similar mechanism of action to amphotericin. It has a high toxicity and cannot be used systematically. Nystatin is typically used topically, but also may be used orally for *oropharyngeal* or *esophageal candidiasis* ("swish and swallow").

▼Table 5–4.7 Antifungal Drugs

Drugs	Mechanism of Action	Clinical Applications	Pharmacokinetics & Interactions	Toxicities
Amphotericin B	***Binds to ergosterol*** in fungal cell membranes, forming "leaky pores"	Candidemia and infections caused by *Aspergillus, Blastomyces, Cryptococcus, Histoplasma, Mucor,* etc.	Multiple forms, IV for systemic infections (liposomal forms less ***nephrotoxic);*** topical for ocular/bladder infections	Nephrotoxicity is dose-limiting, ***additive with other nephrotoxic drugs;*** infusion reactions (chills, fever, muscle spasms, hypotension)
Azoles Ketoconazole Fluconazole Itraconazole Posaconazole Voriconazole	***Inhibit fungal P450-dependent enzymes*** blocking ergosterol synthesis; resistance can occur with long-term use	Aspergillosis (voriconazole); blastomycosis (itraconazole, fluconazole); mucormycosis (posaconazole); alternative drugs in candidemia and infections caused by *Aspergillus, Blastomyces, Cryptococcus,* and *Histoplasma*	Various topical and oral forms for dermatophytoses; oral, parenteral forms for mycoses (fluconazole, itraconazole, posaconazole, voriconazole); most azoles undergo hepatic metabolism; fluconazole eliminated in urine unchanged	Ketoconazole rarely used in systemic fungal infections owing to its inhibition of hepatic and adrenal P450s; other azoles are less toxic, but may cause GI upsets and rash; voriconazole causes visual disturbances and is class D for pregnancy risk
Echinocandins Caspofungin Micafungin Anidulafungin	***Inhibit β-glucan synthase*** decreasing fungal cell wall synthesis	Treatment of candidemia; caspofungin is also used as "salvage" therapy in apergillosis	IV forms; micafungin increases levels of nifedipine and cyclosporine	Gastrointestinal (GI) distress, flushing from histamine release
Flucytosine	***Inhibits DNA and RNA polymerases; prodrug activated to 5-Fμ***	Synergistic with amphotericin B in candidemia and cryptococal infections	Oral; enters cerebrospinal fluid; renal elimination	Bone marrow suppression
Terbinafine	Inhibits epoxidation of squalene	Mucocutaneous fungal infections; accumulates in keratin	Oral; long duration of action (weeks)	GI upsets, headache

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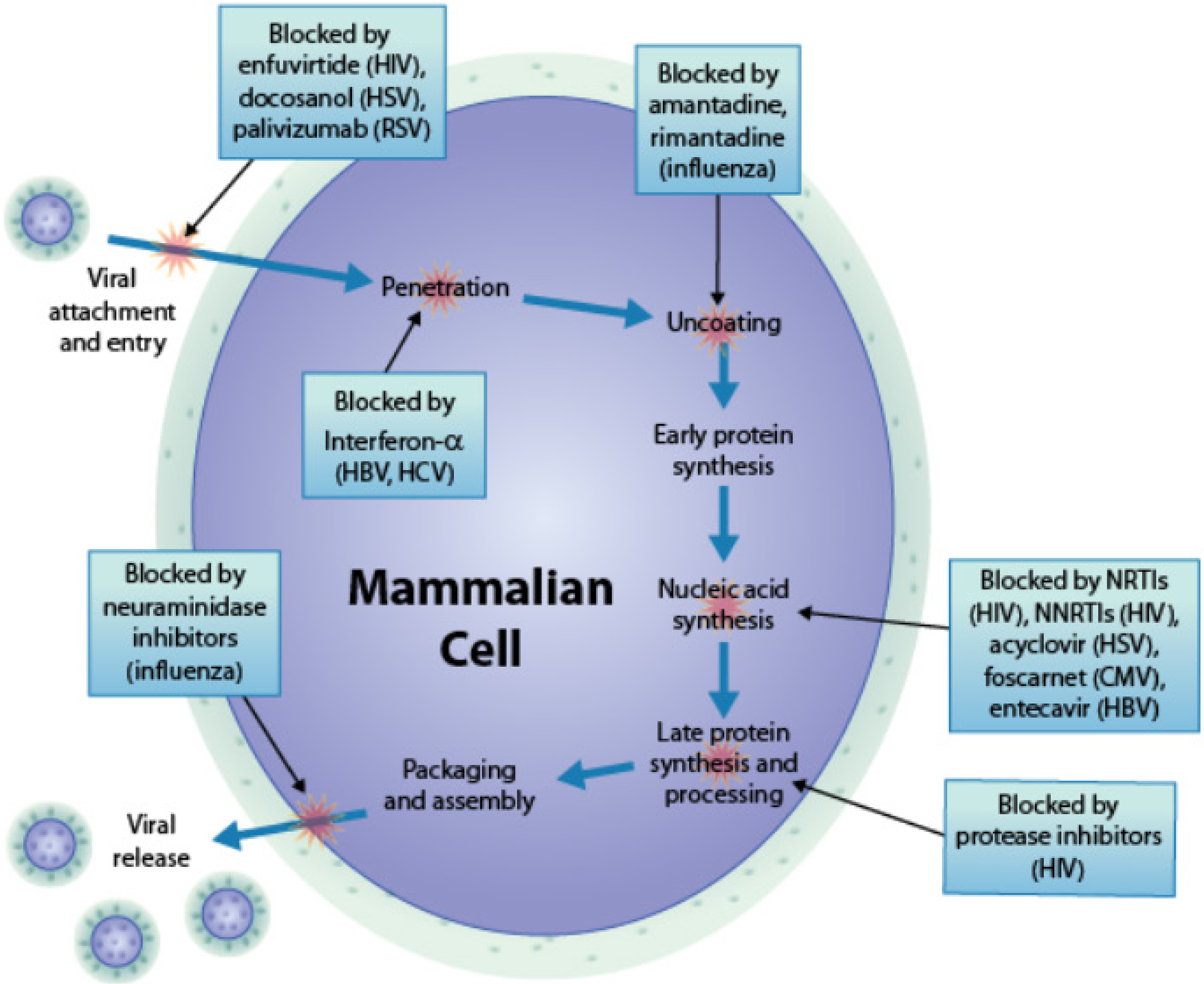
5 Antiviral Drugs

Clinical use of antiviral drugs increased in the 1990s and 2000s, particularly with the advent of anti-HIV therapy. Areas of high-yield focus for Step 1 include drugs used to treat HIV and the herpesvirus family (HSV, CMV).

5.1 Overview of Antiviral Agents

Antiviral agents may be used to treat active infections or to provide prophylaxis against infections, as used with immunocompromised patients. These agents fall into two broad categories: antimetabolites and agents that target unique viral proteins.


Blocked by enfuvirtide (HIV), docosanol (HSV), palivizumab (RSV)
Blocked by amantadine, rimantadine (influenza)
Viral attachment and entry
Penetration
Uncoating
Blocked by Interferon-α (HBV, HCV)
Early protein synthesis
Blocked by neuraminidase inhibitors (influenza)
Mammalian Cell
Nucleic acid synthesis
Blocked by NRTIs (HIV), NNRTIs (HIV), acyclovir (HSV), foscarnet (CMV), entecavir (HBV)
Late protein synthesis and processing
Packaging and assembly
Viral release
Blocked by protease inhibitors (HIV)

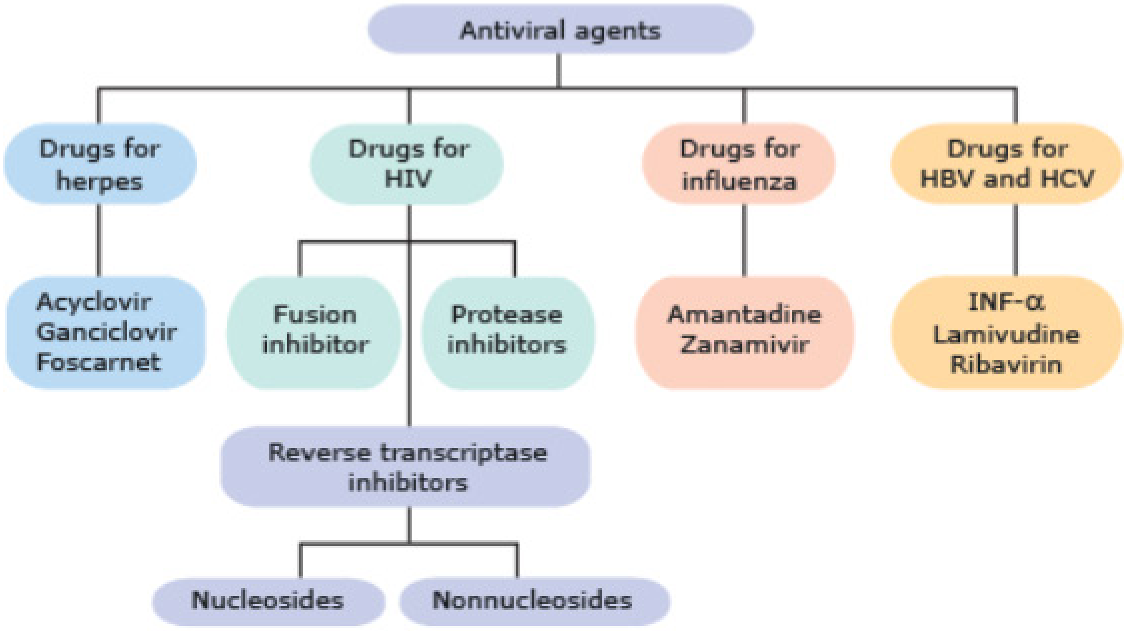
▲ **Figure 5-5.1A** Sites of Antiviral Drug Action

5.1.1 Antimetabolites

Many antiviral agents are *antimetabolites* chemically related to naturally occurring purine and pyrimidine bases. In general, these drugs require *metabolic activation* and, once activated, *interfere with DNA or RNA synthesis/replication*. Resistance to antimetabolites is often due to viruses acquiring mutations that prevent activation of antimetabolite drug.

5.1.2 Drugs Targeting Viral Proteins

A number of the antiviral agents target proteins unique to viruses, such as *HIV protease* or the influenza virus *neuraminidase*. Ideally, antiviral agents are selective toward viral proteins and do not interfere with host cell activity.


Antiviral agents
Drugs for herpes
Drugs for HIV
Drugs for influenza
Drugs for HBV and HCV
Acyclovir
Ganciclovir
Foscarnet
Fusion inhibitor
Protease inhibitors
Amantadine
Zanamivir
INF-α
Lamivudine
Ribavirin
Reverse transcriptase inhibitors
Nucleosides
Nonnucleosides

▲ **Figure 5-5.1B** Antiviral Agents

5.2 Drugs Targeting Herpesviruses

Herpesvirus can be clinically serious and require antiviral therapy. Most of the drugs used to treat herpesvirus infections are not active against all herpesviruses but selective toward some viruses in this family.

5.2.1 Overview of Herpesvirus Family

The herpesvirus family includes *herpes simplex viruses* (HSV-1 and HSV-2), *cytomegalovirus* (CMV), *varicella-zoster virus* (VZV), *Epstein-Barr virus* (EBV), and some emerging pathogens such as human herpesvirus 6 or HHV-6. Infection with herpesviruses is very common throughout the population, often causing minimal issues. Immunocompromised individuals, however, can have clinically severe infections.

5.2.2 Acyclovir, Valacyclovir, and Famciclovir

These three agents are all members of the guanosine analog antiviral family. Famciclovir is not commonly used, but has similar properties and a similar spectrum of activity to acyclovir.

Mechanism of Action Acyclovir is an *antimetabolite* that is converted to an active form by *viral thymidine kinase*. The active form interferes with viral DNA polymerase by acting as a chain terminator.

Pharmacokinetics Acyclovir is usually given intravenously due to low bioavailability. Valacyclovir, administered orally, is a prodrug that converts to acyclovir in vivo.

Resistance Mechanisms Resistance occurs due to mutations in thymidine kinase. These mutations often lead to resistance to acyclovir, ganciclovir, and famciclovir.

Spectrum of Activity Acyclovir is used to treat active HSV and VZV infections, including HSV encephalitis, neonatal HSV infection, herpes zoster, and HSV or VZV infections in immunocompromised patients. Valacyclovir is used to treat genital herpes (usually caused by HSV-2), herpes zoster, and to prevent viral infection in immunocompromised patients.

Adverse Effects The most serious side effects associated with acyclovir are bone marrow suppression and *crystalluria*. Crystalluria is associated with intravenous acyclovir and can be prevented by *adequate hydration* during infusions. Neurologic side effects (delirum, tremor, seizures) are rarely associated with acyclovir, valacyclovir, or famciclovir therapy.

5.2.3 Ganciclovir and Valganciclovir

Ganciclovir and valganciclovir are used for prophylaxis and treatment of *CMV infection,* especially in immunocompromised patients. Ganciclovir also decreases the incidence of Kaposi sarcoma in AIDS patients, probably due to activity against HHV-8.

Mechanism of Action Ganciclovir and valganciclovir have similar mechanism of action to acyclovir.

Pharmacokinetics Ganciclovir has very low bioavailability—less than 10%—and is administered intravenously. Valganciclovir is a prodrug of ganciclovir that is given orally.

Resistance Mechanisms Resistance occurs due to mutations in *thymidine kinase*. These mutations often lead to cross-resistance to acyclovir and famciclovir.

Spectrum of Activity Ganciclovir and valganciclovir have much better activity against CMV than acyclovir or famciclovir. Ganciclovir is not used against HSV or VZV infections.

Adverse Effects The major adverse effect to ganciclovir is *bone marrow toxicity,* which can lead to *anemia, thrombocytopenia,* and *neutropenia*. Intravenous ganciclovir is more likely to cause adverse effects compared to oral valganciclovir.

5.2.4 Foscarnet

Foscarnet is a second-line agent for CMV infections including CMV retinitis. Foscarnet also is used for HSV and VZV infections resistant to acyclovir or famciclovir.

Mechanism of Action Foscarnet directly inhibits herpesvirus DNA polymerase. It also is active against HIV by inhibiting HIV reverse transcriptase.

Pharmacokinetics Foscarnet has poor bioavailability and is administered intravenously. It deposits in bone and thus may persist in the body for long periods.

Resistance Mechanisms Resistance to foscarnet occurs due to mutations in *DNA polymerase* (herpesvirus) or reverse transcriptase (HIV). Because foscarnet is not an antimetabolite, there is no cross-resistance with acyclovir or ganciclovir.

Spectrum of Activity Foscarnet has good activity against CMV, HSV, and VZV.

Important Concept

Acyclovir, valacyclovir, and famciclovir have good activity against HSV and VZV, but generally poor activity against CMV. Ganciclovir and valganciclovir have much better activity against CMV than acyclovir or famciclovir.

Adverse Effects The major limiting effect for foscarnet is *nephrotoxicity*, classically presenting with abnormalities in calcium, magnesium, and phosphorus levels. Central nervous system symptoms also can occur.

5.3 HIV Therapies

HIV therapy has expanded greatly since the introduction of zidovudine (AZT) decades ago.

5.3.1 Overview of HIV Therapy

The two main targets for HIV therapy are *viral reverse transcriptase (RT)* and the *aspartate protease*. A newer class of medications targets proteins involved in viral entry or fusion with the host cell. *Highly Active Antiretroviral Therapy (HAART)* has become a standard therapy for HIV infection. The principle of HAART is to combine drugs from different classes to reduce the risk of drug resistance. Many HAART regimens constitute three or four drugs from at least two different classes. Clinical indications for starting HAART are AIDS-defining illness such as Kaposi sarcoma, CD4 count less than 350 CD4+ cells/μL, or high viral load.

5.3.2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

NRTIs are mainstays of HIV therapy and are commonly used in HAART regimens. For Step 1, it is worth knowing details about the most commonly used NRTIs, which include:

- Zidovudine (AZT)
- Didanosine (ddI)
- Lamivudine (3TC)
- Stavudine (d4T)
- Abacavir (ABC)
- Emtricitabine (FTC)

Mechanism of Action The NRTIs are antimetabolites that get activated by conversion to a *triphosphate* form. NRTIs incorporate into viral DNA and cause chain termination.

Pharmacokinetics The NRTIs are generally well absorbed following oral administration and are eliminated by both hepatic metabolism and renal clearance.

Resistance Mechanisms Resistance occurs due to mutations in the *HIV RT enzyme*. Specialized laboratory testing can predict resistance based on the mutations detected.

Spectrum of Activity NRTIs have activity against most HIV strains, although resistance is a challenging clinical problem.

Adverse Effects All NRTIs are associated with the risk of *liver toxicity,* hepatitis steatosis, and lactic acidosis. Therapy should be stopped in cases of rising liver enzymes or hepatomegaly. *Neurotoxicity* (agitation, seizures, periphery neuropathy) also has been reported.

Zidovudine Zidovudine (AZT) was introduced in the mid-1990s and is the prototype NRTI. Despite all the years that have passed since zidovudine's introduction, it is still effective against HIV-1 and HIV-2. Zidovudine has a higher incidence of neurologic adverse effects than other NRTIs. The drug also is prone to causing bone marrow toxicity, an effect not commonly seen with other NRTIs. Zidovudine is recommended for treatment and prophylaxis of HIV in pregnant women.

Didanosine Didanosine was the second drug to gain approval for HIV therapy. Due to inactivation by stomach acid, didanosine is given as special buffered formulation and taken on an empty stomach. The adverse effect unique to didanosine is pancreatitis, which may manifest as abdominal pain and rising serum levels of lipase or amylase.

Important Concept

Clinically significant adverse effects associated with NRTIs include bone marrow toxicity for zidovudine and pancreatitis for didanosine.

5.3.3 Nucleotide Analogs

The nucleotide analogs have the subtle difference from NRTIs of already containing phosphate groups. So far, there is only a single drug—tenofovir—in this class, and it is used in a number of combination therapy tablets for HIV treatment. Tenofovir also is used to treat chronic hepatitis B infection.

Mechanism of Action Like NRTIs, tenofovir blocks reverse transcriptase, thereby causing *chain termination* of viral DNA.

Pharmacokinetics Tenofovir is administered orally. The drug inhibits the metabolism of didanosine, thereby increasing plasma concentrations of didanosine.

Resistance Mechanisms Resistance is uncommon, but has been reported due to mutations in the RT enzyme of HIV.

Spectrum of Activity Tenofovir is very commonly used for HIV therapy and also for hepatitis B virus.

Adverse Effects Tenofovir classically causes gastrointestinal symptoms. A less common side effect is renal tubular damage with electrolyte abnormalities.

5.3.4 Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Although not used as widely as NRTIs, NNRTIs are used regularly in many HIV regimens, including HAART. The three most common NNRTIs are:

- Nevirapine
- Efavirenz
- Delavirdine

Mechanism of Action NNRTIs are direct inhibitors of the active RT enzyme.

Pharmacokinetics Many NNRTIs are metabolized by the cytochrome P450 (CYP) 3A4 enzyme, and some also are inhibitors or inducers of this same enzyme.

Resistance Mechanisms Resistance occurs due to mutations in the RT enzyme.

Spectrum of Activity In contrast to NRTIs, NNRTIs are *not* active against HIV-2, due to differences in the RT enzyme in HIV-2. Thus, NNRTIs are used only to treat HIV-1 infections.

Adverse Effects Because many NNRTIs are metabolized by the CYP3A4, complex drug-drug interactions can occur between these agents if more than one is used in combination and other drugs, such as cyclosporine and ethinyl estradiol, that are also metabolized by CYP3A4. The NNRTIs are also prone to causing skin rashes, including, rarely, Stevens-Johnson syndrome.

Nevirapine Nevirapine is a widely employed NNRTI used for general HIV-1 therapy as well as with *pregnant women* in labor to *prevent the spread of HIV-1 to the neonate*.

Efavirenz Efavirenz is also widely used. The classic adverse effect for efavirenz comprises CNS symptoms such as dizziness, somnolence, and depression.

5.3.5 HIV Protease Inhibitors

HIV protease inhibitors are widely used for HIV-1 and HIV-2 therapy, including HAART regimens. There are many proteases on the market, including:

- Saquinavir (prototype)
- Indinavir
- Ritonavir
- Nelfinavir
- Atazanavir
- Darunavir
- Fosamprenavir
- Lopinavir
- Tipranavir

Mechanism of Action The protease inhibitors *inhibit the aspartate protease of HIV*. Proteases are responsible for cleavage of the Gag-Pol polyprotein into the building blocks of new viruses. Blocking the protease *stops viral reproduction*.

Pharmacokinetics The protease inhibitors are predominantly metabolized by *CYP3A4*. Consequently, drugs that induce CYP3A4, such as phenytoin and carbamazepine, or inhibit it, such as erythromycin, may alter plasma concentrations of the protease inhibitors.

Resistance Mechanisms Resistance is due to mutations in the Gag-Pol polyprotein.

Spectrum of Activity Protease inhibitors are active against both HIV-1 and HIV-2, and do not require intracellular activation.

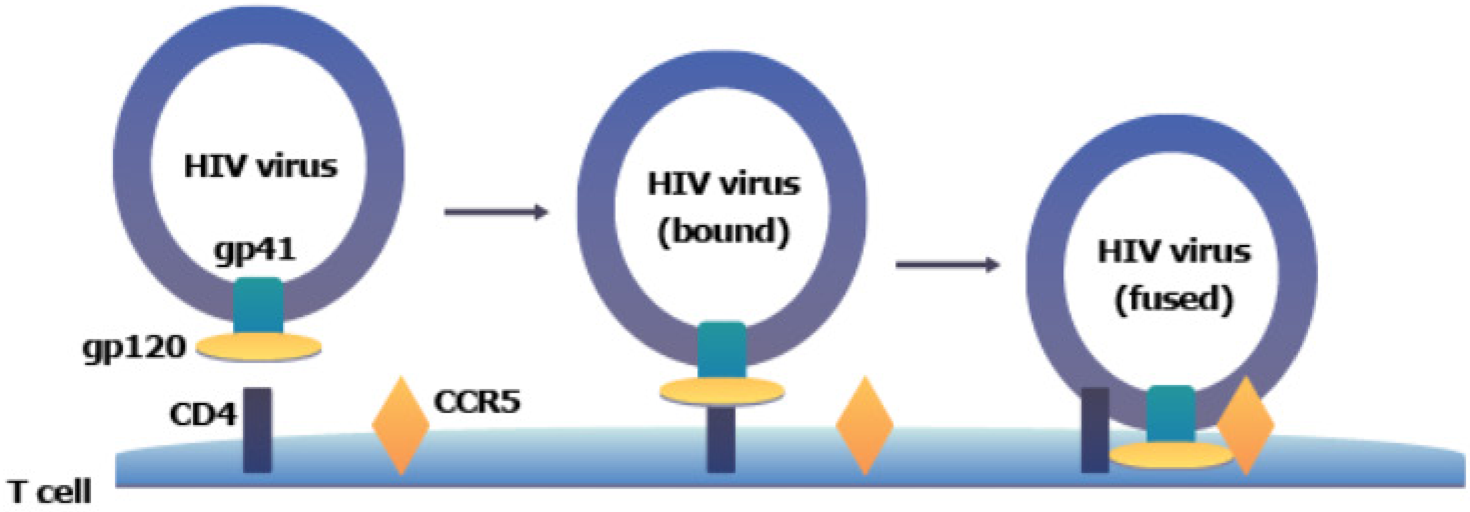
Adverse Effects The main adverse effect of protease inhibitors is *lipodystrophy,* a syndrome of disordered lipid and carbohydrate metabolite. This resembles metabolic syndrome, "Syndrome X," with insulin resistance, central obesity, and increased plasma lipids. Fat deposition in the neck, peripheral and facial wasting, and breast enlargement in men are also seen. Therapy also may be complicated by hepatitis or pancreatitis. Due to metabolic adverse effects, physicians tend to avoid use of protease inhibitors in children.

Saquinavir Saquinavir is the prototype protease inhibitor and is typically given in combination with ritonavir. This combination takes advantage of inhibition of CYP3A4, which allows less costly saquinavir to be used because its metabolism is slowed by ritonavir. Saquinavir is the protease inhibitor that is least prone to causing lipodystrophy.

5.3.6 Entry/Fusion Inhibitors (Enfuvirtide, Maraviroc)

Entry and fusion inhibitors represent a novel approach to HIV therapy and thus complement the older reverse transcriptase and protease inhibitors. In fact, these agents are approved as "salvage therapy" for patients not responding to RT or protease inhibitors.

Mechanism of Action The HIV virus gains entry to T lymphocytes through its gp160 molecule binding to CD4. Once binding occurs, the gp120 subunit can then bind to CCR5 or CXCR4 chemokine receptors. Viral entry then occurs via gp41. Entry/fusion inhibitors block this process: enfuvirtide by binding with gp41, and maraviroc by binding with CCR5.



▲ **Figure 5-5.3** HIV Antiviral Entry/Fusion Inhibitors

Pharmacokinetics Of the two drugs currently in this class, enfuvirtide is given by subcutaneous injection. As a peptide, it is eventually broken down into amino acids and cleared. Maraviroc is primarily metabolized by CYP3A4.

Resistance Mechanisms Resistance to enfuvirtide is due to mutations in gp41.

Spectrum of Activity Both enfuvirtide and maraviroc are active against HIV-1 only. Maraviroc is even more specific in being active against only the R5 form of HIV-1.

Adverse Effects Enfuvirtide and maraviroc can cause allergic reactions and eosinophilia.

Enfuvirtide Enfuvirtide is a peptide drug that binds to gp41 and *prevents fusion of HIV-1 to CD4-positive lymphocytes*.

Maraviroc Maraviroc is a synthetic molecule that binds to CCR5 specifically. It is effective for only the R5 form of HIV-1 ("CCR-tropic"). A fairly high fraction of patients who fail HAART therapy have the R5 subtype of HIV-1.

5.3.7 Integrase Inhibitors (Raltegravir)

Integrase inhibitors are the newest class of HIV drugs. So far, raltegravir is the only drug in this class to reach the market. Raltegravir was approved in 2007 for "salvage therapy" of both HIV-1 and HIV-2 infections.

Mechanism of Action Raltegravir blocks *integrase,* a viral enzyme that incorporates HIV DNA into the cell.

Pharmacokinetics Raltegravir shows extensive pharmacokinetic variability. Antacids lower the bioavailability.

Resistance Mechanisms Mutations of viral integrase have been shown to confer resistance.

Spectrum of Activity Raltegravir is active against both HIV-1 and HIV-2.

Adverse Effects Raltegravir has an excellent side effect profile, with gastrointestinal symptoms being the most common.

5.3.8 HAART Regimens

HAART regimens are *combinations of three or more agents from at least two different classes of anti-HIV medications*. HAART regimens shift over time due to resistance patterns, so it is difficult to know what regimens might appear on Step 1 questions. The key for Step 1 is to recognize what might constitute a valid regimen. For example, a regimen consisting of three protease inhibitors (no NRTI or NNRTI) or of only one or two drugs would not qualify as HAART.

Standard Regimens Examples of common HAART regimens are:

- Lopinavir/ritonavir, zidovudine, lamivudine
- Lopinavir/ritonavir, tenofovir, emtricitabine
- Efavirenz, zidovudine, lamivudine

Pediatric Regimens Pediatric HAART regimens tend to *avoid protease inhibitors* due to the lipodystrophy adverse effects. The efavirenz, zidovudine, and lamivudine regimen mentioned above would be one possibility for a pediatric regimen.

5.4 Drugs for Treating Influenza

Several drugs are available to treat influenza. Keep in mind that vaccination is the primary preventive therapy currently used.

5.4.1 Amantadine and Rimantadine

Amantadine and rimantadine are effective against influenza A virus and are used as either prophylaxis or for treatment of active infection. Both drugs interfere with the viral proton ion channel M2 and also *block uncoating of the viral RNA*. Unfortunately, most strains of influenza in the United States are resistant to amantadine/rimantadine due to mutations in the M2 protein. The main adverse effects are related to increased *dopamine release*, such as nervousness, light-headedness, and insomnia.

5.4.2 Oseltamivir and Zanamivir

Oseltamivir (Tamiflu) and zanamivir (Relenza) are similar drugs that inhibit the *neuraminidase* of influenza A and B. Oseltamivir is given orally; zanamivir by inhalation. Neuraminidases break the bond between newly formed virus and the host cell, allowing for spread of virus to other cells. Oseltamivir and zanamivir are 70% to 90% effective in preventing disease when given promptly and also can reduce the duration of active infection.

5.5 Drugs for Treating Hepatitis and Other Viruses

A number of agents are effective in treating viral hepatitis.

5.5.1 Ribavirin

Ribavirin is an antiviral drug with a wide spectrum of activity. Use of this drug is limited by its severe adverse effects.

Mechanism of Action Ribavirin is a *guanosine analog* that is phosphorylated within the host cell to an active form that interferes with production of GTP.

Pharmacokinetics Ribavirin is absorbed by nucleoside transporters in the gastrointestinal tract. Once absorbed, it has a very wide volume of distribution, becoming trapped as the phosphate form in cells. *Ribavirin penetrates the CSF*.

Resistance Mechanisms Resistance to ribavirin is rare, but has been reported in hepatitis C virus (mechanism unknown).

Spectrum of Activity Ribavirin is active against a number of viruses and is used for treatment of:

- Hepatitis C
- Respiratory syncytial virus (RSV)
- Hantavirus and other hemorrhagic fevers
- West Nile virus

Adverse Effects Ribavirin commonly causes *hemolytic anemia* (20% of users) and also can cause depression, fatigue, and irritability. The drug is a known teratogen, and *pregnant women* (including health care workers) should *avoid all exposure*. This is especially an issue with treatment of RSV by aerosol "tent," where pregnant women may get passively exposed to the vapor. Women exposed to ribavirin should wait six months before attempting to conceive.

5.5.2 Interferons

Interferons are cytokine proteins released by lymphocytes in response to multiple types of infection. Three major interferons (α, β, and γ) are found in humans.

Mechanism of Action Interferons bind to receptors on cells and "warn" them of impending infection. Interferons cause decreased protein synthesis, increased MHC expression, and increased apoptosis, in addition to hundreds of other cellular effects.

Pharmacokinetics The interferons are poorly absorbed orally and are administered by intravenous injection.

Resistance Mechanisms Resistance to interferon-α has been reported in hepatitis C virus due to mutations in the protein of the viral envelope.

Spectrum of Activity Interferon-α is available in injectable forms for treatment of *chronic hepatitis B and C infections*. It is often coadministered with ribavirin for treatment of hepatitis C. Interferon-α is also used to treat *hairy cell leukemia, chronic myelogenous leukemia* (although imatinib and related drugs are now first-line), and some *lymphomas*. Interferon-β is used for treatment of multiple sclerosis. Interferon-γ has fewer clinical applications than interferon-α and -β, but is used for chronic granulomatous disease and osteopetrosis.

Adverse Effects The adverse effects of interferon-α can be severe and include a "flu-like" syndrome; mood changes, with rare cases of suicidality reported; and cardiotoxicity. Interferon-β also can cause a flu-like syndrome. Seizures are a rare but severe adverse effect.

5.5.3 Imiquimod

Imiquimod is not technically an antiviral agent, but as an immune response modulator it is used to treat a variety of skin conditions, including those with a viral pathology.

Mechanism of Action Imiquimod activates immune cells through Toll-like receptor 7 (TLR7). This causes the release of interferon-α, interleukin-6 and tumor necrosis factor-α.

Pharmacokinetics Imiquimod is administered as external cream.

Resistance Mechanisms Resistance to imiquimod is rare.

Spectrum of Activity Imiquimod is approved for the treatment of external genital warts, actinic keratosis, and basal cell carcinoma. It is also effective at treating *molluscum contagiosum*.

Adverse Effects Nonspecific inflammation and dermatitis are the most common adverse effects.

▼Table 5–5.5 Antivirals and Antiretrovirals

Drug Class	Mechanism of Action	Clinical Applications	Pharmacokinetics & Interactions	Toxicities
ANTIVIRAL DRUGS **Antiherpes drugs** Acyclovir Valacyclovir (prodrug) Penciclovir Famciclovir (prodrug)	Activated by viral thymidine kinase (TK) to forms that inhibit viral DNA polymerase	Treatment and prophylaxis for HSV-I, HSV-2, and VZV	Acyclovir: Topical oral, and IV Penciclovir: Topical Famciclovir and valcyclovir: Oral	Oral forms cause nausea, diarrhea, and headache; IV acyclovir may cause renal and CNS toxicity
Drugs for cytomegalovirus Ganciclovir Valganciclovir Cidofovir Foscarnet	Viral activation of ganciclovir to form inhibiting ***DNA polymerase;*** no viral bioactivation of cidofovir and foscarnet	Treatment of CMV infections in immunosuppression (e.g., AIDS) and organ transplantation	Ganciclovir: Oral, IV, intraocular forms Valganciclovir: Oral Cidofovir, foscarnet (IV)	Ganciclovir: Bone marrow suppression, hepatic and neurologic dysfunction Cidofovir and foscarnet: Nephrotoxicity Forscarent: CNS effects and electrolyte imbalance
Antihepatitis drugs Interferon-α (IFN-α) Adefovir-dipivoxil Entecavir Lamivudine Ribavirin	Degrades viral RNA via activation of host cell RNAase (IFN-α); inhibition of HBV polymerase (others); multiple antiviral actions (ribavirin)	Suppressive treatment of HBV (all drugs except ribavirin); treatment of HCV (ribavirin +/− IFN-α)	IFN-α: Parenteral Adefovir, entacavir, lamivudine, and ribavirin: Oral Ribavirin: Inhalational	IFN-α: Alopecia, myalgia, depression, flu-like syndrome Adefovir: Lactic acidosis, renal and hepatic toxicity Ribavirin: Anemia, teratogen
Anti-influenza drugs Amantadine Rimantadine Oseltamivir Zanamivir	Amantadine and rimantidine; block of M2 proton channels; Oseletamivir and zanamivir inhibit neuraminidase	M2 blockers virtually obsolete; others prophylaxis vs. most current flu strains and shorten symptoms	Oral forms except zanamivir (inhalational)	Oseltamivir: Gastrointestinal effects Zanamivir: Bronchospasm in asthmatics

(continued on next page)

▼Table 5–5.5 Antivirals and Antiretrovirals (continued)

Drug Class	Mechanism of Action	Clinical Applications	Pharmacokinetics & Interactions	Toxicities
ANTIRETROVIRAL DRUGS				
Nucleoside/ nucleotide reverse transcriptase inhibitor (NRTIs)[1] Abacavir Didanosine Emtricitabine Lamivudine Stavudine Tenofovir Zalcitabine Zidovudine	Inhibit HIV reverse transcriptase after phosphorylation by cellular enzymes; cross-resistance common, but incomplete	Duration of action usually longer than half-life; most undergo renal elimination, especially didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zidovudine	Zidovudine: Bone marrow suppression Abacavir: Hypersensitivity Didanosine: Pancreatitis Stavudine, zalcitabine: Peripheral neuropathy	Most NRTIs are not extensively metabolized by hepatic enzymes such as the CYP450 isoforms, so they have few interactions that concern their pharmacokinetic characteristics
Nonnucleoside reverse transcriptase inhibitors (NNRTIs) Delavirdine Efavirenz Etravirine Nevirapine	Inhibit HIV reverse transcriptase; no phosphorylation required; cross-resistance between NNRTIs but not with NRTIs	All current NNRTIs are metabolized via CYP450 isozymes; etravirine may induce formation of CYP3A4, but inhibits other CYP450s	Delavirdine, nevirapine: Rash, increased liver enzymes Efavirenz: Teratogenicity	Inducers of CYP450 isozymes (e.g., phenytoin, rifampin) and inhibitors (e.g., azoles, PIs) alter NNRTI duration of action; note etravirine
Protease inhibitors (PIs)[2] Atazanavir Darunavir Fosamprenavir Indinavir Nelfinavir Ritonavir Saquinavir Tipranavir	Inhibit viral protein processing;cross-resistance between PIs common	Elimination mainly via metabolism by CYP450 isozymes; they act as substrates and inhibitors of P450; Fosamprenavir is a prodrug forming amprenavir, a substrate and inducer of CYP450	Atazanavir, fosamprenavir, lopinavir, nelfinavir, saquinavir: GI distress and diarrhea Atazanavir: Peripheral neuropathy Amprenavir: Rash Indinavir: Hyperbilirubinemia and nephrolithiasis	Ritonavir[3] and other PIs can inhibit CYP450 metabolism of many drugs including antihistamines, antiarrythmics, HMG-CoA reductase inhibitors, oral contraceptives, and sedative-hypnotics; drugs known to induce or inhibit CYP450 isoforms may alter the plasma levels of PIs
Early inhibitors Enfuvirtide Maraviroc	Block fusion between viral and cellular membranes (enfuvirtide); CCR5 receptor antagonist (maraviroc)	Extrahepatic hydrolysis of enfuvirtide (subcutaneous injection); P450 metabolism (maraviroc)	Enfuvirtide: Hypersensitivity Maraviroc: Muscle/ joint pain, diarrhea, and increased liver enzymes	Inducers and inhibitors of CYP450 alter elimination of maraviroc; no effects on enfuvirtide

[1] **NRTIs, nucleoside/nucleotide reverse transcriptase inhibitors: Risk of lactic acidosis with hepatic steatosis is characteristic of the group.**
[2] **PIs, inhibitors: Risk of hyperlipidemia, fat maldistribution, hyperglycemia, and insulin resistance is characteristic of the group, with possible exception of fosamprenavir.**
[3] **Ritonavir is a potent inhibitor of the 3A4 isoform of CYP450, an action used to advantage in "boosting" effects of other PIs. Drug–drug interactions between PIs and many other medications occur commonly.**

Trevor, Anthony et al, *Katzung & Trevor's Pharmacology Examination and Board Review*, 9th ed. © 2010 The McGraw-Hill Companies, Inc.

6 Antiparasitic Drugs

Antiparasitic drugs cover a wide range. For Step 1 review, the highest-yield topics are drugs used to treat malaria, toxoplasmosis, trypanosomiasis, and leishmaniasis.

6.1 Antimalarials

Antimalarials are used both for prophylaxis of malaria and also to treat active infection. Some of the drugs are most effective in the erythrocytic phase and others (principally primaquine) are more effective in the hepatic (liver) phase.

6.1.1 Forms of Malaria

Four species of *Plasmodium* (*P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*) cause human disease. *P. falciparum* usually causes the most severe infection.

6.1.2 Chloroquine

Chloroquine is a quinine derivative widely used for malaria prophylaxis and treatment.

Mechanism of Action Chloroquine disrupts the pH of the *Plasmodium* digestive vacuole and interferes with the parasite's ability to digest hemoglobin.

Pharmacokinetics Chloroquine is well absorbed orally and has a very wide volume of distribution. Deposits of chloroquine into tissues, particularly in the retina, can cause adverse effects.

Resistance Mechanisms Chloroquine resistance is a major limitation and is mediated by mutations in the drug transport PfCRT. Due to resistance, chloroquine is used as prophylaxis only in areas without chloroquine resistance, in the Caribbean and in Central America north of the Panama Canal.

Spectrum of Activity Chloroquine is very good at treating the active, erythrocytic phase of all four species of *Plasmodium,* but not effective in eradicating the liver phase. Chloroquine alone is usually insufficient to cure infection with *P. vivax* or *P. ovale*.

Adverse Effects Side effects are relatively uncommon and include hemolytic anemia in G6PD-deficient patients and visual disturbances (retinopathy with high doses). Long-term use can cause neuropathies.

Important Concept

Chloroquine is effective against the active, erythrocytic phase of the *Plasmodium* species, but not the liver phase. Primaquine is effective against the liver phase of all four *Plasmodium* species.

6.1.3 Primaquine

Primaquine is a quinine derivative used for both prophylaxis and the treatment of malaria.

Mechanism of Action Primaquine shares a similar mechanism of action with chloroquine.

Pharmacokinetics Primaquine is well absorbed following oral administration.

Resistance Mechanisms Resistance to primaquine by *Plasmodium vivax* has been reported. Mechanism is unclear.

Spectrum of Activity In contrast to chloroquine, primaquine is effective in eradicating the liver phase of all four strains of malaria. Primaquine is also used as "terminal prophylaxis" for patients who have traveled to areas where *P. ovale* and *P. vivax* are endemic. This is intended to prevent latent infection. Primaquine and chloroquine are often used together to eradicate *P. ovale* and *P. vivax* infection. Primaquine is also occasionally used along with clindamycin as an alternative treatment of *Pneumocystis jiroveci* pneumonia in patients who cannot tolerate trimethoprim-sulfamethoxazole.

Adverse Effects Primaquine has a high risk of *hemolytic anemia in G6PD-deficient patients*.

6.1.4 Mefloquine

Mefloquine is used extensively in areas with chloroquine-resistant malaria. Adverse neuropsychiatric effects are the main limitation.

Mechanism of Action Mefloquine has a similar mechanism of action to chloroquine.

Pharmacokinetics Mefloquine is well absorbed following oral administration and predominantly eliminated by liver metabolism. The drug should be avoided by patients with liver failure.

Resistance Mechanisms Mefloquine resistance in *P. falciparum* has been reported in Southeast Asia and is apparently due to increased expression of the PFMDR1 gene.

Spectrum of Activity Mefloquine is very effective against *P. falciparum* and *P. malariae*. It is not active against the hepatic phase. Mefloquine is widely used as malaria prophylaxis in areas with chloroquine resistance.

Adverse Effects Mefloquine is limited by *severe neuropsychiatric reactions* that can include hallucinations, psychosis, seizures, and encephalopathy.

6.1.5 Atovaquone and Proguanil

Atovaquone and proguanil are second-line therapy for malaria.

Mechanism of Action Atovaquone inhibits mitochondrial electron transport. Proguanil inhibits the *Plasmodium* dihydrofolate reductase. Each drug is largely ineffective when used alone due to resistance. The combination of atovaquone and proguanil is very effective.

Pharmacokinetics Atovaquone is highly lipophilic, and gastrointestinal absorption is greatly increased by taking the drug with milk or food. Elimination is by both liver metabolism and renal clearance.

Resistance Mechanisms Mutations in cytochrome b confer resistance to atovaquone. Use of the combination product (atovaquone-proguanil) limits resistance.

Spectrum of Activity Atovaquone and proguanil are predominantly used as treatment and prophylaxis for chloroquine-resistant *P. falciparum*. These two drugs are also used in combination therapy for *Pneumocystis* infection.

Adverse Effects Atovaquone and proguanil may elevate liver function tests and can cause influenza-like side effects.

6.1.6 Other Antimalarial Drugs

Due to resistance and/or adverse effects of the quinine derivatives, other drugs are sometimes used to treat malaria.

Doxycycline Doxycycline is used for prophylaxis and treatment of multidrug P. falciparum.

Pyrimethamine Pyrimethamine is similar to proguanil and is used in combination with sulfadoxine for treatment and prophylaxis of malaria in Africa.

Artesunate/Artemether Artesunate/artemether are derivatives of Chinese herbal drugs and used for severe P. falciparum infections. These drugs are not yet approved by the FDA and are available only by contacting the CDC.

6.2 Drugs for Intestinal Parasites

Common intestinal parasites include protozoans, amoebas, and helminths, the last of which are covered separately below.

6.2.1 Metronidazole and Tinidazole

Metronidazole and tinidazole are the drugs of choice for several parasitic infections in addition to their role in treating anaerobic bacterial infections. Tinidazole has similar efficacy, but is more expensive than metronidazole.

Mechanism of Action Metronidazole and tinidazole are taken up by protozoa or anaerobic bacteria and converted to a toxic metabolite by ferro-reduction.

Pharmacokinetics Both drugs can be given either orally or intravenously.

Resistance Mechanisms Resistance to these drugs is rare.

Spectrum of Activity Metronidazole and tinidazole are effective treatment for:

- Amebiasis (Entamoeba histolytica)
- Giardiasis (Giardia lamblia)
- Trichomoniasis (Trichomonas)

Adverse Effects Metronidazole has an unpleasant taste and can also cause a disulfiram-like reaction with ethanol due to inhibition of aldehyde dehydrogenase.

Important Concept

The two primary options for anaerobic infections are clindamycin and metronidazole.

6.2.2 Iodoquinol

Iodoquinol is effective against amebic organisms in the intestinal lumen.

Mechanism of Action The action of iodoquinol is unclear.

Pharmacokinetics Iodoquinol has very low absorption through the gastrointestinal tract and is thus used to eradicate parasites within the intestines.

Resistance Mechanisms Some *Entamoeba histolytica* have resistance to iodoquinol due to overexpression of the P-glycoprotein pump.

Spectrum of Activity Iodoquinol is predominantly used for amebic dysentery.

Adverse Effects Iodoquinol contains iodine and can cause allergic reactions. Neurotoxicity is a rare side effect.

6.3 Drugs for Toxoplasmosis

Toxoplasmosis is a common parasitic infection. The most vulnerable populations are immunocompromised patients and pregnant women (especially those without prior exposure).

6.3.1 Criteria for Prophylactic Therapy

Prophylactic therapy in AIDS patients is generally started when CD4 count is below 100/mm^3.

6.3.2 Pyrimethamine and Clindamyin or Sulfadiazine

Pyrimethamine-clindamycin or pyrimethamine-sulfadiazine are the primary treatments and prophylaxis for *Toxoplasma gondii*. Adverse effects of pyrimethamine can include folic acid depletion. Hypersensitivity reactions can also occur.

6.4 Drugs for Trypanosomiasis

Trypanosomes cause African sleeping sickness and Chagas disease. The drugs used to treat these two types of trypanosomal infections are quite distinct.

6.4.1 *Trypanasoma brucei* (African Sleeping Sickness)

African sleeping sickness is caused by transmission of *Trypanosoma brucei* by the tsetse fly. In the early stages, the organisms replicate in blood and lymph. In the later stages, the organisms invade the CNS, leading to inflammation, progressive lethargy, coma, and eventual death.

The drug protocol of choice for early stage is *suramin* combined with *pentamidine*. Suramin has an unclear mechanism of action but is associated with several CNS and bone marrow toxicities. Late stage of African sleeping sickness is very difficult to treat. Melarsoprol is an arsenic-containing drug that can cause death due to toxicity. Melarsoprol should be reserved for severe cases.

6.4.2 *Trypanasoma cruzi* (Chagas Disease)

Chagas disease is caused by transmission of *Trypanosoma cruzi* by the reduviid bug. The organism can invade cardiac myocytes and nervous plexi of the esophagus and colon. Long-term complications include *megaesophagus* (potentially leading to *achalasia*), megacolon, and *dilated cardiomyopathy*.

Nifurtimox, the traditional treatment, is no longer available in the United States. Melarsoprol is the most effective option, but carries risk of severe toxicity (even death) as described above. Benznidazole is a newer antibiotic that has an unclear mechanism of action.

6.5 Drugs for Leishmaniasis

Leishmaniasis affects an estimated 12 million people worldwide. The two major forms of leishmaniasis are cutaneous and visceral. Visceral leishmaniasis, also known as kala-azar, can present with massive hepatosplenomegaly and can be fatal.

6.5.1 Stibogluconate

Stibogluconate is the main drug used for treating leishmaniasis. It is an unusual compound that contains the element antimony; hence the *Stibo*. The pentavalent antimony inhibits glycolysis in the parasite. Stibogluconate is active in all forms of leishmaniasis, including cutaneous, mucocutaneous, and visceral effects. This antiparasitic agent must be administered intravenously and can produce toxic cardiac effects, including prolongation of the QT interval.

6.5.2 Alternative Drugs for Leishmaniasis

In the event that stibogluconate cannot be used, alternative agents include pentamidine for visceral leishmaniasis and fluconazole or metronidazole for cutaneous lesions.

▼**Table 5–6.5** Common Protozoans and Their Treatment

Organism	Transmission	Symptoms	Diagnosis	Treatment
Trypanosoma brucei	Tsetse fly	Sleeping sickness; cardiac failure	Hemoflagellate in blood or lymph node	Suramin: East African Pentamidine: West African Melarsoprol: severe
T. cruzi	Reduviid (kissing) bug	Chagas disease: megacolon, cardiac failure	Hemoflagellate in blood or tissue	Nifurtimox or ***benznidazole***
Leishmania donovani	Sand fly	Visceral leishmaniasis granulmatous skin lesions	Intracellular (macrophages) leishmanial bodies	Stibogluconate or amphotericin, pentamidine
Plasmodium falciparum	Female anopheline mosquito	Malarial paroxysm: chills, fever, headache, nausea cycles	Plasmodia in RBC, typical of the species involved	Quinine derivatives or artesuate Atovaquone/ proguanil
Toxoplasma gondii	Oral from cat fecal material; or meat	Adult: flu like Congenital: abortion, neonatal blindness and neuropathies	Intracellular (in macrophages) tachyzoites	***Pyrimethamine*** plus sulfa or clindamycin

6.6 Anthelminthic Drugs

The helminths include a broad spectrum of worm-like parasites. Helminths can be classified into three groups: nematodes (roundworms), trematodes (flukes), and cestodes (tapeworms). The drugs used to treat these parasites are often effective against multiple organisms.

- **Nematodes**: Common parasites include *Ascaris*, *Filarioidea*, two species of hookworms, *Enterobius* (pinworms), *Trichuris trichiura* (whipworms), and *Trichinella spiralis*.
- **Trematodes**: Noteworthy examples include *Schistosoma* and *Fasciola* (formerly *Clonorchis*) *hepatica*.
- **Cestodes**: Clinically important species include *Taenia solium* (pork tapeworm), *Taenia saginata* (beef tapeworm), and *Diphyllobothrium* latum (fish tapeworm).

6.6.1 Albendazole

Albendazole is a widely used anthelminthic drug that blocks glucose uptake and microtubule assembly within parasites. This anthelmin has a wide spectrum of activity and is the primary drug for ascariasis, hookworm, pinworm, and whipworm infections. Albendazole is also active against the pork tapeworm in the larval stage (cysticercosis). Adverse effects can include alopecia and elevated levels of liver enzyme, but the drug is generally well tolerated.

6.6.2 Mebendazole

Mebendazole is similar to albendazole, blocking glucose uptake and microtubule assembly. This anthelmin is a primary drug for treatment of ascariasis, pinworm, and whipworm infections. The main adverse effect is gastrointestinal irritation but agranulocytopenia and alopecia have been reported when the drug is used at high dosages.

6.6.3 Thiabendazole

Thiabendazole is closely related to mebendazole in structure, targeting parasites in the same way as that drug and albendazole. It is active against strongyloidosis and trichinosis but is not a first-line drug because its adverse effects—which include hematuria, allergic reactions (including Stevens-Johnson syndrome), and liver failure—are worse than alternative drugs. Thiabendazole should not be used to treat pregnant women and patients with liver or kidney problems.

6.6.4 Ivermectin

Invermectin is a first-line therapy for nematode infections, including onchocerciasis, cutaneous larva migrans, and strongyloidosis. This anthelmin enhances GABA neurotransmission in nematodes, causing their paralysis. Because ivermectin does not cross the blood-brain barrier, CNS side effects are not seen. Ivermectin is often used in single-dose treatments, and adverse effects are often related to reactions to dying worms, including rashes, pruritus, fever, hypotension, and joint pain. These symptoms often can be minimized by pre-therapy with NSAIDs and antihistamines. Ivermectin should not be used in pregnant women due to teratogenic potential.

6.6.5 Diethylcarbamazine

Diethylcarbamazine, which paralyzes microfilariae by an unknown mechanism, is used to treat infections caused by this parasitic nematode. It is the drug of choice for filarial infections caused by *Brugia malayi*, *Wuchereria bancrofti,* and *Loa loa* (the nematode responsible for eye worm disease). Common adverse effects include headache, weakness, and malaise. As with ivermectin, reactions to dying parasites can trigger allergic reactions. These symptoms can have clinical significance with onchocerciasis.

6.6.6 Pyrantel Pamoate

Pyrantel pamoate is commonly used for nematode infections. It activates nicotinic acetylcholine receptors within parasites, causing persistent muscle contraction followed by depolarized paralysis. Pyrantel pamoate is highly active against adult nematode worms, but not their eggs. It is the drug of choice for hookworm and roundworm infections, but is inactive against tapeworms and flukes. The drug is poorly absorbed and is generally well tolerated, but can cause gastrointestinal side effects.

▼**Table 5-6.6A** Common Nematodes and Their Treatment

Organism	Transmission	Symptoms	Diagnosis	Treatment
Ascaris lumbricoides	Orofecal	Abdominal pain, weight loss, distended abdomen	Stool; corticoid oval egg	Mebendazole, albendazole, pyrantel pamoate
Trichinella spiralis	Poorly cooked pork	Depends on worm location and burden: gastroenteritis; edema, muscle pain, spasm; eosinophilia, tachycardia, fever, chill, headache, vertigo, delirium, coma, etc.	Medical history, eosinophilia, muscle biopsy, serology	Mebendazole or albendazole; add corticosteroids for severe infection
Enterobius vermicularis	Orofecal	Perianal pruritus, rare abdominal pain, nausea, vomiting	Stool: embryonated eggs, flat on one side	Pyrantal pamoate or mebendazole
Necator americanes; Ancylostoma duodenale (Hookworms)	Orofecal (egg); skin penetration (larvae)	Maculopapular erythema (ground itch), broncho-pneumonitis, epigastric pain, GI hemorrhage, anemia, edema	Stool: oval segmented eggs	Mebendazole

6.6.7 Praziquantel

Praziquantel is a first-line medication for fluke infections. This agent increases membrane permeability to calcium, leading to muscle contractions followed by paralysis and parasite death. Praziquantel is highly active against most trematodes. It is the treatment of choice for schistosomiasis, intestinal flukes, and beef, pork, and fish tapeworms. Praziquantel is generally well tolerated. Neurologic adverse effects can be seen in the treatment of neurocysticercosis, with corticosteroids often used as pretreatment.

▼**Table 5-6.6B** Common Trematodes and Their Treatment

Organism	Transmission	Symptoms	Diagnosis	Treatment
S. mansoni, S. japonicum	Skin penetration by cercariae	Dermatitis, abdominal pain, bloody stool, periportal fibrosis, hepatosplenomegaly, ascites, CNS	Eggs in stool: *S. mansoni*—large lateral spine *S. japonicum*—small lateral spine	Praziquantel
Schistocoma hematobium	Skin penetration by cercariae	Dermatitis, urogenital cystitis, urethritis, and squamous cell bladder carcinoma	Eggs in urine: Large terminal spine	Praziquantel
Fasciolopsis buski	Metacercariae on water chestnut	Epigastric pain, nausea, diarrhea, edema, ascites	Eggs in stool	Praziquantel
Clonorchis sinensis	Cysts in raw fish	Inflammation and deformation of bile duct, hepatitis, anemia, and edema; risk of cholangiocarcinoma	Eggs in stool	Praziquantel, albendazole

6.6.8 Niclosamide

Niclosamide is a second-line treatment of beef, pork, and fish tapeworms and an alternative drug for small and large intestinal flukes. This anthelminthic is thought to act by uncoupling oxidative phosphorylation within parasites. Adverse effects are usually mild, although, as with other anthelminthics, allergic reactions from dying parasites can occur.

▼**Table 5-6.6C** Common Cestodes and Their Treatment

Organism	Transmission	Symptoms	Diagnosis	Treatment
Taenia saginata	Cyst in beef	Epigastric pain, vomiting, diarrhea	Proglottids or eggs in stool or perianal area	Praziquantel, mebendazole, niclosamide
Taenia solium	Cyst in pork	Epigastric pain, vomiting, diarrhea	Proglottids or eggs in stool of perianal area	Praziquantel, niclosamide
Cysticercosis	Orofecal	Muscle pain and weakness, ocular and neurologic problems	Proglottids or eggs in stool of perianal area	Praziquantel, niclosamide
Diphyllobothrium latum	Cyst in fish	Adbominal pain, loss of weight, anorexia, malnutrition and B_{12} deficiency problems	Proglottids or eggs in stool of perianal area	Praziquantel
Echinococus glanulosus	Orofecal	Large cysts produce various symptoms depending on the location of the organism	MRI/CT, anti-hydatid fluid anitbody (EIA), Casoni skin test	Albendazole, ethanol injection surgery
E. multilocularis	Orofecal	As above	As above	Surgery, albendazole

Chapter 5 Review Questions

1. A 22-year-old female patient presents to an outpatient clinic with dysuria of two days' duration. Urinalysis reveals elevated white blood cells and many bacteria. Urine Gram stain shows plump gram-negative rods. The patient has a past history of anaphylactoid-type reaction with sulfa medications. Based on the most likely etiology for her symptoms, what is the *most appropriate* pharmacotherapy?

A. Meropenem
B. Trimethoprim-sulfamethoxazole
C. Penicillin G
D. Ciprofloxacin
E. Trimethoprim

The following vignette applies to questions 2 and 3.

A 28-year-old male presents with spiking fevers, malaise, left-sided chest pain, and cough. His symptoms started two weeks ago and have worsened despite a course of intravenous oxacillin. He has a known history of intravenous drug abuse. On examination, he has a temperature of 39.2°C, heart rate of 120 bpm, and respiratory rate of 30. Chest x-ray reveals pneumonia and right-sided pleural effusion.

2. What is the mechanism of action for the *most appropriate* pharmacotherapy?

A. Inhibition of folate synthesis
B. Inhibition of mycolic acid synthesis
C. Detergent disruption of the bacterial cell membrane
D. Inhibition of dephosphorylation of a carrier molecule for peptidoglycans
E. Prevention of chain elongation and cross-linking by binding to the D-ala-D-ala terminus

3. Due to difficulty with gaining intravenous access, the patient needs to be treated with a medication that is effective by oral administration. Which of the following medications represents the *most effective* treatment for this patient?

A. Tinidazole
B. Vancomycin
C. Tobramycin
D. Dicloxacillin
E. Linezolid

Review Questions Chapter 5

The following vignette applies to questions 4 and 5.

A 45-year-old HIV-positive male presents with dyspnea, non-productive cough, and fever. Physical exam reveals a male who appears ill and cachectic. A chest x-ray shows diffuse air-space opacities. Because the patient is markedly dyspneic and is requiring supplemental oxygen, empiric antimicrobial therapy is begun.

4. What of the following diagnostic procedures would be *most likely* to reveal the etiology of his respiratory tract infection?

A. Sputum culture
B. Bronchoalveolar lavage
C. Throat swab
D. Lymph node biopsy
E. Pleurocentesis

5. Which of the following drugs is the *best* pharmacotherapy for his respiratory infection?

A. Vancomycin
B. Metronidazole
C. Imipenum
D. Cephalothin
E. Trimethoprim-sulfamethoxazole

6. A 45-year-old woman is admitted to the intensive care unit for respiratory distress. She visited her relatives in Russia six months ago and acquired tuberculosis during her visit. Her current medications include isoniazid, rifampin, ethambutol, and pyrazinamide. Drug susceptibilities are pending. Which pharmacotherapy would be *most appropriate* to add to her current regimen of treatment?

A. Chloramphenicol
B. Metronidazole
C. Streptomycin
D. Doxycyclinev
E. Trimethoprim-sulfamethoxazole

7. A 21-year-old female with acute lymphoblastic leukemia is receiving induction chemotherapy. Her fever spikes to 39.8°C. She is given broad coverage for bacterial, fungal, and viral infections. Her fever improves within 48 hours; however, by day three her serum creatinine has risen to 2.2 mg/dL from a baseline of 1.1 mg/dL. Which of the following drugs is *most likely* to have caused this problem?

A. Itraconazole
B. Cephalothin
C. Nystatin
D. Amphotericin B
E. Penicillin

Chapter 5 Review Questions

The following vignette applies to questions 8 and 9.

A 24-year-old woman is treated with clindamycin for cellulitis. The patient completes her therapy as directed but several days later develops profuse, watery diarrhea, which progresses to bloody stools. She presents to the acute care clinic appearing quite ill with a temperature of 40°C. Her skin is flushed and very warm to the touch.

8. What diagnostic test would best confirm the *most likely* diagnosis in a reasonable amount of time?

A. Stool culture
B. Identification of specific bacterial toxin in the stool
C. Blood culture
D. Gram stain of breast milk from the patient
E. Rectal examination

9. Which of the following antibiotics is *most likely* to be effective pharmacotherapy for this patient?

A. Metronidazole
B. Ceftriaxone
C. Tetracycline
D. Chloramphenicol
E. Trimethoprim-sulfamethoxazole

10. A 22-year-old woman presents to the gynecologic clinic because of vaginal discharge and vulvar pruritis for six days. She is allergic to penicillin. She has a thin, foamy, pale green vaginal discharge. A wet mount preparation shows a mobile, pear-shaped, flagellated organism. A pregnancy test is negative. What is the *most appropriate* pharmacotherapy for this patient?

A. Griseofulvin
B. Ceftriaxone
C. Doxycycline
D. Metronidazole
E. Clotrimazole vaginal tablets

Review Questions Chapter 5

11. A 25-year-old male with HIV/AIDS is being treated with multiple drugs, including didanosine, indinavir, zidovudine, trimethoprim-sulfamethoxazole, and lamivudine.

Fasting plasma laboratory studies prior to starting therapy:

Total cholesterol	180 mg/dL
Low-density lipoprotein	100 mg/dL
High-density lipoprotein	50 mg/dL
Triglycerides	150 mg/dL
Glucose	75 mg/dL
Creatinine	0.6 mg/dL

Fasting plasma laboratory studies two months into therapy:

Total cholesterol	250 mg/dL
Low-density lipoprotein	175 mg/dL
High-density lipoprotein	35 mg/dL
Triglycerides	200 mg/dL
Glucose	150 mg/dL
Creatinine	0.7 mg/dL

Which of the drugs that this patient is taking is the *most likely* cause of the changes in laboratory values?

A. Didanosine
B. Indinavir
C. Zidovudine
D. Trimethoprim-sulfamethoxazole
E. Lamivudine

12. A 29-year-old woman presents to the acute care clinic because of vaginal discharge, vulvar pruritus, and burning for three days. The vagina is tender and erythematous. A potassium hydroxide wet mount preparation shows spores and pseudohyphae. What would be the *most appropriate* pharmacotherapy given *intra-vaginally?*

A. Miconazole
B. Griseofulvin
C. Amphotericin B
D. Spectinomycin
E. Acyclovir

Chapter 5 Review Questions

The following vignette applies to questions 13 and 14.

A 24-year-old female returned 10 days ago from a one-week trip to Central Africa. She has complained of fever and chills for the past week and is now hospitalized.

13. Which of the following diagnostic tests or procedures is *most likely* to reveal the etiology of her disease?

A. Peripheral blood smear
B. Blood culture
C. Sputum culture
D Bronchoalveolar lavage with silver stain
E. Chest x-ray

14. What is the *most appropriate* pharmacotherapy?

A. Stibogluconate
B. Pyrimethamine-sulfadiazine
C. Mefloquine
D. Thiabendazole
E. Niclosamide

15. A 19-year-old female college student presents to the student health clinic because of fever and multiple painful blisters on her vulva for three days. She admits to unprotected sexual intercourse with a new partner several times over the past three weeks. There are shallow ulcers on her vulva, vaginal mucosa, and cervix. What is the *most appropriate* pharmacotherapy?

A. Valacyclovir
B. Intravenous immunoglobulin (IVIG)
C. Interferon-β
D. Foscarnet
E. Ganciclovir

Review Answers Chapter 5

1. The correct answer is D. Ciprofloxacin. This is a urinary tract infection most likely caused by *E. coli* or another member of the *Enterobacteriaceae.* The first-line agent is trimethoprim-sulfamethoxazole (Bactrim). However, the patient is sulfa allergic, so an oral fluoroquinolone such as ciprofloxacin (Cipro) is an acceptable alternative. Other alternatives include nitrofurantoin (an antibiotic which concentrates in the urine), doxycycline, or various cephalosporins. Treatment with trimethoprim alone is not recommended due to the frequent resistance of the *Enterobacteriaceae* to this agent when it is used alone. Even though meropenem would cover *E. coli* infection, this agent requires *intravenous therapy,* which would be cumbersome, and would be expensive and needlessly invasive for an otherwise healthy patient presenting in the outpatient setting. Penicillin G does not provide good coverage of the organisms causing urinary tract infections.

2. The correct answer is E. Prevention of chain elongation and cross-linking by binding to the D-ala-D-ala terminus. This clinical history strongly suggests infection by methicillin-resistant *Staphylococcus aureus.* Intravenous drug abusers are at high risk for this infection through the use of contaminated needles. The patient's symptoms are more severe than the typical "walking pneumonia" produced by *Mycoplasma pneumoniae. Clostridium difficile* infection would have gastrointestinal symptoms. *Escherichia coli* and *Candida albicans* would not commonly produce the symptoms seen. Vancomycin inhibits chain elongation and cross-linking by binding to the D-ala-D-ala terminus.

3. The correct answer is E. Linezolid. In addition to vancomcyin, linezolid and quinupristin/dalfopristin are used to treat MRSA. For treatment of MRSA, vancomycin must be given intravenously due to lack of oral absorption (the only indication for oral vancomycin is treatment of pseudomembranous colitis). Linezolid may be given orally or intravenously. Dicloxacillin cannot be used because of resistance. The other choices are not effective against MRSA. This patient is at high risk for endocarditis and should be evaluated by echocardiography.

4. The correct answer is B. Bronchoalvelolar lavage. The clinical history and radiologic findings strongly suggest pneumonia caused by *Pneumocystis jiroveci* (formerly *P. carinii*). The complete workup of this individual would likely include a CD4 count that would probably be less than 250/mm^3. The diagnostic specimen of choice to diagnose *Pneumocystis* infection is bronchoalveolar lavage (BAL). Sputum and throat swabs are inferior specimens for diagnosis of *Pneumocystis.* The other choices are not appropriate for diagnosis of *Pneumocystis* infection.

5. The correct answer is E. Trimethoprim-sulfamethoxazole (Bactrim) is first-line therapy for pneumonia caused by *Pneumocystis carinii.* Pentamidine is also effective against *Pneumocystis carinii* and would be an acceptable alternative if trimethoprim-sulfamethaxazole could not be used (e.g., because of a sulfa drug allergy).

6. The correct answer is C. Streptomycin is used in five drug regimens for tuberculosis or in place of ethambutol in four drug regimens. The clinical scenario suggests multidrug-resistant tuberculosis. Occasionally, clinicians use streptomycin in three drug regimens for disseminated disease or tuberculous meningitis. Other options for multidrug-resistant tuberculosis include cycloserine and fluoroquinolones.

7. The correct answer is D. Amphotericin B ("Amphoterrible") can cause a variety of renal problems, including decreased creatinine clearance. Amphotericin will not usually cause permanent renal damage in patients without preexisting renal impairment, unless total lifetime doses of 3 to 4g are exceeded. The liposomal preparation of amphotericin is less likely to cause these problems, although it is extremely expensive. The other group of antibiotics strongly associated with nephrotoxicity is the aminoglycosides (e.g., gentamicin).

Chapter 5 Review Answers

8. The correct answer is B. Identification of specific bacterial toxin in the stool. This vignette is a classic story for pseudomembranous colitis, which is most commonly caused by *Clostridium difficile. C. difficile* commonly inhabits the bowel without causing trouble. However, treatment with antibiotics (especially clindamycin) can disrupt the bowel flora and permit *C. difficile* to proliferate. *C. difficile* produces toxins that can damage the bowel (leading to bloody stools and a yellowish "pseudomembrane") and make the patient quite ill, sometimes with an almost septic appearance. Specific tests to identify the toxin in the stools are the diagnostic tests of choice.

9. The correct answer is A. Metronidazole (Flagyl) is effective therapy against *C. difficile.*

10. The correct answer is D. Metronidazole (Flagyl) is the first-line therapy for vaginitis caused by trichomoniasis. Her sexual partners also should be treated.

11. The correct answer is B. Indinavir, and other inhibitors of HIV protease, are associated with a *lipodystrophy syndrome* of central obesity, elevated triglycerides, elevated LDL and total cholesterol, and, sometimes, insulin-dependent diabetes mellitus (with elevated fasting glucose). These side effects are a major drawback to this otherwise extremely effective class of anti-retroviral drugs.

12. The correct answer is A. Miconazole. This is an episode of vaginal candidiasis. There are multiple over-the-counter and prescription drugs that can be applied intra-vaginally to treat this infection. These include clotrimazole, miconazole, and butoconazole.

13. The correct answer is A. Peripheral blood smear. The clinical history is most suggestive of malaria. Examination of peripheral blood smear looking for parasite forms is the most appropriate diagnostic tests.

14. The correct answer is C. Mefloquine is one of the front-line therapies for malaria.

15. The correct answer is A. Acyclovir. This is an episode of genital herpes (most likely caused by herpes simplex virus, HSV, type 2) for which valacyclovir is the recommended therapy. This will usually shorten the length of the episode but will not prevent recurrences. Foscarnet is a second-line therapy for HSV infections due to its adverse effect profile, and would be used only if valacyclovir or acyclovir were ineffective. Ganciclovir has better activity against cytomegalovirus than HSV.

CHAPTER 6 Chemotherapeutic and Anti-Rejection Drugs

1 Overview of Anticancer Agents

A diverse array of medications is used to treat cancer. Many of the drugs inhibit cell proliferation, which can be effective against rapidly dividing tumors, but with potential adverse effects on normal host cells. Other drugs, especially some newer agents (such as imatinib), target proteins unique to certain cancers. For Step 1 review, focus on established chemotherapy agents and newer drugs with significant impact. Adverse effects of chemotherapeutic agents are high yield for Step 1.

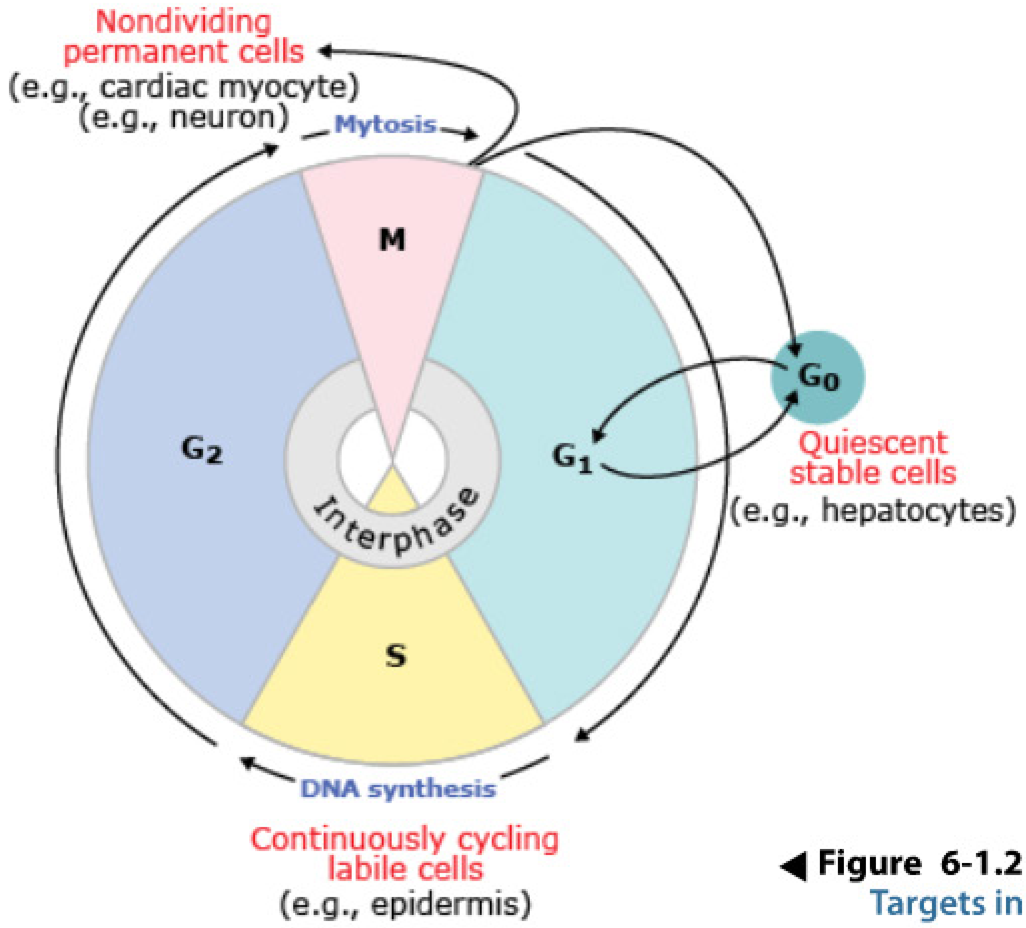
1.1 Effects on Rapidly Proliferating Cells

Many of the traditional chemotherapy agents interfere with cell cycle processes, thereby damaging rapidly proliferating cells. This can be therapeutically useful in *targeting aggressive cancers* such as leukemias. However, normal host cells that divide frequently can also sustain damage. The tissues most commonly affected by chemotherapy include:

- Bone marrow
- Gastrointestinal tract mucosa
- Hair follicles
- Gonads
- Skin

1.2 Cell Cycle

Many of the traditional chemotherapeutic agents target different points of the cell cycle.


Nondividing permanent cells
(e.g., cardiac myocyte)
(e.g., neuron)
Mytosis
M
G2
Interphase
G1
G0
Quiescent stable cells
(e.g., hepatocytes)
S
DNA synthesis
Continuously cycling labile cells
(e.g., epidermis)

◀ **Figure 6-1.2** Chemotherapeutic Targets in the Cell Cycle

USMLE® Key Concepts

For Step 1, you must be able to:

- Describe the mechanism of action and common therapeutic uses of cancer chemotherapy agents and anti-rejection drugs.
- List the adverse effects associated with cancer chemotherapy agents and anti-rejection drugs.
- Explain the therapeutic options for managing chemotherapy-induced cytopenias.

1.3 Common Adverse Effects of Chemotherapeutic Agents

Adverse effects of chemotherapeutic agents commonly relate to damage to rapidly dividing host cells. Such adverse effects include *bone marrow suppression, alopecia* (damage to hair follicles), *diarrhea* or *gastrointestinal bleeding* (injury to GI mucosa), *infertility* (damage to gonads), and *skin rash*. Injury to bone marrow can be especially serious and lead to life-threatening complications. Cancers themselves may impact bone marrow function, either by direct infiltration or by affecting other organs that regulate bone marrow, as when a kidney injury leads to a lack of erythropoietin.

1.3.1 Neutropenia

Injury to leukocyte lineages can lead to neutropenia (low neutrophil count). Neutropenia *increases the risk of infection*, particularly to bacteria. Neutropenia is difficult to manage, and a patient presenting with neutropenia and evidence of infection (fever) constitutes a *medical emergency* requiring immediate antibiotic therapy. Low white blood cell count can be managed chronically by granulocyte-colony stimulating factor *(G-CSF)* drugs such as *filgrastim* (Neupogen). Granulocyte transfusions are possible but technically difficult and rarely used. Neutrophils have limited life span, so the therapeutic benefit of granulocyte transfusions is often short-lived.

1.3.2 Thrombocytopenia

Thrombocytopenia (low platelets) is another possible consequence of bone marrow suppression. Thrombocytopenia (especially below 20,000/mL) *increases risk of bleeding,* often presenting as bleeding gums, epistaxis, or gastrointestinal bleeding. If needed, platelet transfusions can be given.

1.3.3 Anemia

Anemia (low red blood cell count) is also commonly seen in cancer patients. For acute management, *packed red blood cell transfusions* may be given. For chronic management, *recombinant erythropoietin* can be administered to stimulate red blood cell production.

Important Concept

On the boards, do not be fooled by an option for whole blood transfusion. Whole blood is essentially never transfused in the U.S. Transfusion therapy involves fractions of whole blood: platelets, plasma, and packed red blood cells.

1.4 Other Treatments for Cancer

Although chemotherapy is used for many cancers, other treatment modalities are used. Surgery, radiation therapy, and *leukapheresis* are examples.

1.4.1 Surgery

Surgery is commonly used for cancers that are fully resectable (such as a discrete breast mass) or to de-bulk large tumors prior to chemotherapy or radiation therapy. The use of chemotherapy following surgery is called *adjuvant chemotherapy*. Chemotherapy prior to surgery is called *neoadjuvant therapy*.

1.4.2 Radiation Therapy

Radiation therapy is used in approximately 50% of all cancer patients. Some tumors, such as seminoma testicular cancers, are very sensitive to radiation therapy and may even be cured by radiation therapy alone. Radiation is also used to shrink tumors, especially those pressing on key structures, such as spine, bone, and esophagus. Radiation therapy may have a palliative effect in reducing symptoms of cancer, such as pain and difficulty eating.

1.4.3 Apheresis

Apheresis is a medical technology in which the blood of a patient or donor is passed through a device that separates out one particular component, such as red blood cells, plasma, platelets, or white blood cells, and returns the remainder to the circulation. *Leukapheresis* (removal of white blood cells) is sometimes used in treatment of leukemias, especially acute leukemias with very high white blood counts. *Plasmapheresis* is used in *Waldenström macroglobulinemia* to remove high levels of IgM that can cause hyperviscosity syndrome.

2

Classes of Chemotherapy Drugs

A chemotherapy drug's class can be useful in understanding its mechanism of action and adverse effects. The main chemotherapy classes include:

- Antimetabolites
- Alkylating agents
- Plant alkaloids
- Antibiotics
- Hormones
- Immunotherapy
- Miscellaneous

2.1 Antimetabolites

The antimetabolites target the *S (synthesis) phase* of the cell cycle by interfering with DNA or RNA processes. A common adverse effect of these drugs is bone marrow suppression.

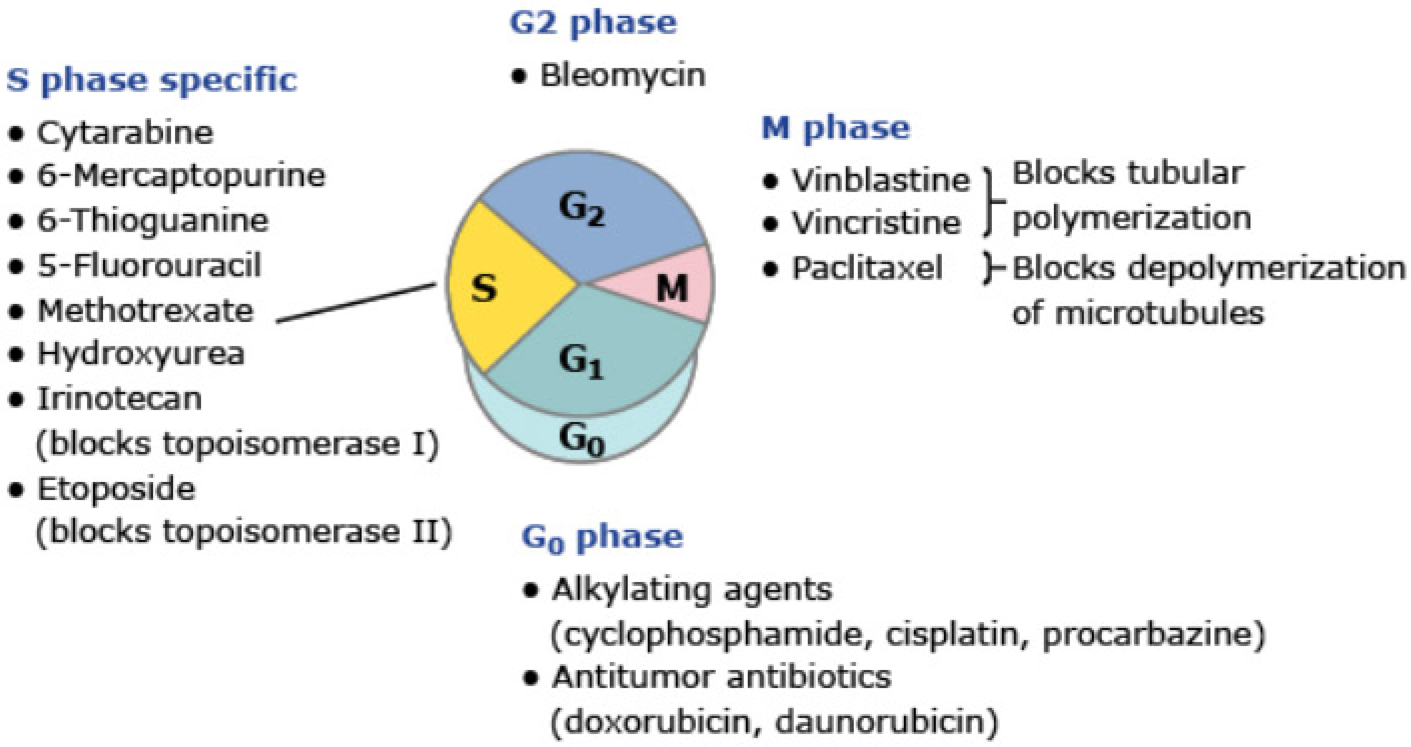
2.1.1 Methotrexate

Methotrexate is used for treatment of acute leukemias, breast carcinoma, lymphomas, and choriocarcinoma. Methotrexate is also used for treatment of severe rheumatoid arthritis and psoriasis, as well as medical management of ectopic pregnancy.

Mechanism of Action Methotrexate *inhibits dihydrofolate reductase,* an enzyme that converts dihydrofolate to the active tetrahydrofolate. Interference with the folate pathway affects the synthesis of thymidine and purines. Methotrexate is highly active against rapidly dividing cells.

Important Concept

Be able to interpret nomograms for Step 1 questions. Another example of a nomogram to know is N-acetylcysteine use in acetaminophen ingestion.


G_2 phase
• Bleomycin
S phase specific
• Cytarabine
• 6-Mercaptopurine
• 6-Thioguanine
• 5-Fluorouracil
• Methotrexate
• Hydroxyurea
• Irinotecan (blocks topoisomerase I)
• Etoposide (blocks topoisomerase II)
G_2
S
M
G_1
G_0
M phase
• Vinblastine
• Vincristine
Blocks tubular polymerization
• Paclitaxel
Blocks depolymerization of microtubules
G_0 phase
• Alkylating agents (cyclophosphamide, cisplatin, procarbazine)
• Antitumor antibiotics (doxorubicin, daunorubicin)

▲ **Figure 6-2.1A** Effect of Cytotoxic Agents on Cell Cycle

Adverse Effects Methotrexate commonly causes bone marrow toxicity. A less common side effect is *crystalluria,* the risk of which can be lessened by adequate hydration during methotrexate infusions. When methotrexate is used at high doses for cancer treatment, *leucovorin (folinic acid)* is often used as an "antidote" or *"rescue"* to limit damage to host cells. Leucovorin is a reduced form of folic acid that can be used by host cells, but not by most tumor cells.

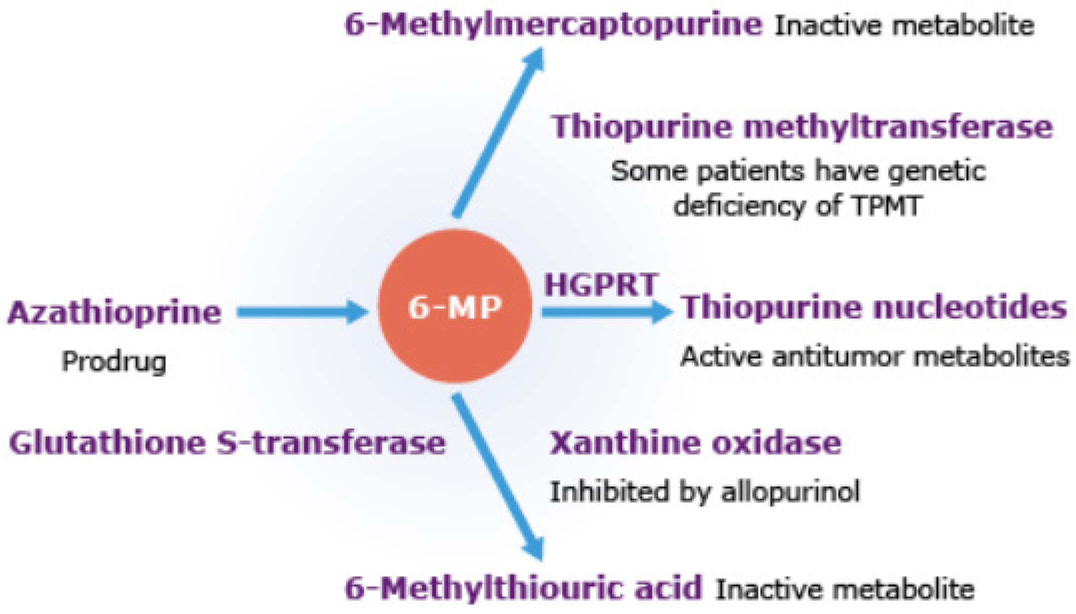
Leucovorin is dosed based on nomograms that relate leucovorin to the plasma concentration of methotrexate at a certain time-point post infusion. For example, in the figure to the right, a methotrexate plasma concentration of 10^{-5} M at 24 hours post infusion requires a leucovorin dose of 100 mg/m^2.

2.1.2 Azathioprine and 6-Mercaptopurine

Azathioprine and 6-mercaptopurine (6-MP) are drugs that inhibit purine (adenine and guanine) metabolism. A *prodrug of 6-MP,* azathioprine is used mainly to treat autoimmune diseases, such as Crohn disease, while 6-MP is used primarily to treat cancers (mainly acute leukemias).

Mechanism of Action 6-MP is activated by the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT) to form abnormal *thiopurine nucleotides* that interfere with purine nucleotide synthesis and metabolism. Tumor cells that lack HGPRT are resistant to azathioprine/6-MP therapy—this is a common reason for acquired resistance. 6-MP is metabolized by thiopurine methyltransferase (TPMT) and *xanthine oxidase* to form inactive metabolites.

Adverse Effects In most individuals, azathioprine and 6-MP are reasonably well tolerated, with bone marrow suppression being the most common adverse effect. However, some patients are deficient in TPMT, one of the two main enzymes that inactivate 6-MP. Such patients are at very high risk for severe bone marrow suppression after administration of 6-MP or azathioprine. This is a *genetic defect* found in approximately 1 in 300 Caucasians of northern European descent. Laboratory testing, either a genetic test or a phenotypic test of *TPMT activity,* is available to identify these patients. Individuals with low TPMT should either not receive azathioprine/6-MP or receive a much lower dose.


6-Methylmercaptopurine Inactive metabolite
Thiopurine methyltransferase
Some patients have genetic deficiency of TPMT
Azathioprine
Prodrug
6-MP
HGPRT
Thiopurine nucleotides
Active antitumor metabolites
Glutathione S-transferase
Xanthine oxidase
Inhibited by allopurinol
6-Methylthiouric acid Inactive metabolite

▲**Figure 6-2.1B** Metabolism of Azathioprine

Connection to Pathology

HGPRT, the enzyme responsible for activating 6-MP, is the same enzyme that is deficient in the rare Lesch-Nyhan syndrome.

2.1.3 Cytarabine (Ara-C)

Cytarabine is an antimetabolite used predominantly in the treatment of acute myeloid leukemia and non-Hodgkin lymphoma.

Mechanism of Action Cytarabine is *activated by tumor cell kinases* to cytosine arabinoside triphosphate, an unnatural nucleotide that damages DNA. Tumor cells that lack the activating kinases are resistant to cytarabine.

Adverse Effects The main adverse effect of cytarabine is bone marrow suppression.

2.1.4 5-Fluorouracil (5-FU)

5-fluorouracil is an antimetabolite that is widely used for treatment of *solid tumors,* especially colon and breast carcinomas.

Mechanism of Action 5-fluorouracil is activated by thymidylate synthase to fluoro-dUMP, a "fake" nucleotide that competes with thymidylate synthase and thus *inhibits DNA synthesis*. Resistant tumor cells have altered thymidylate synthase.

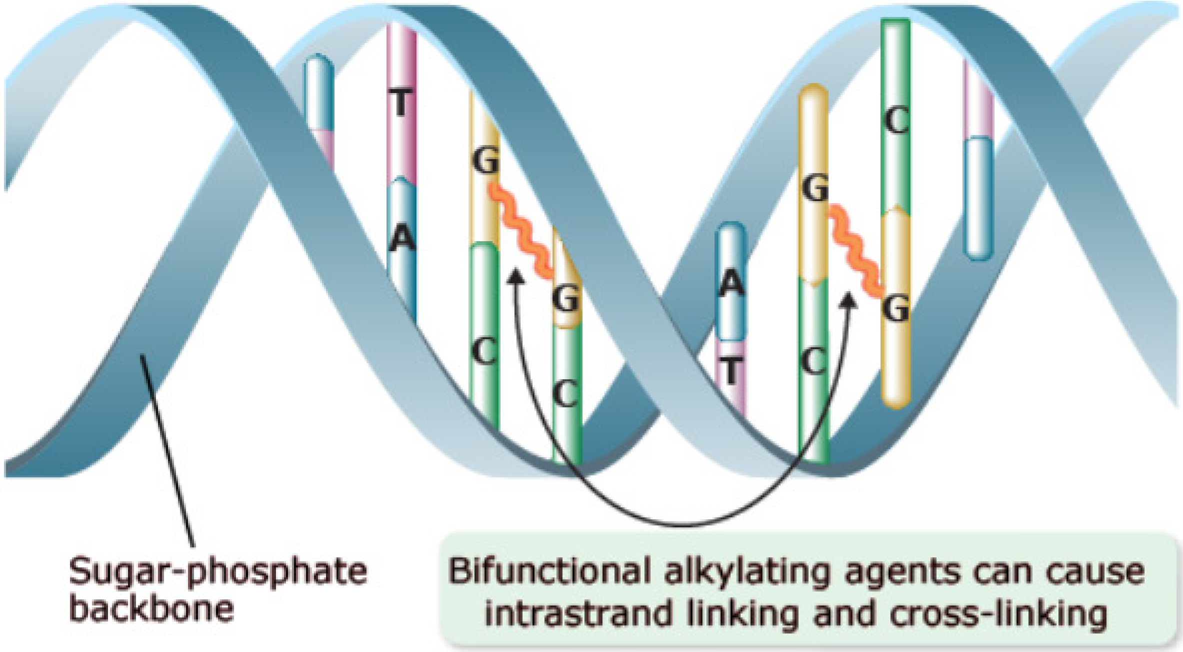
Adverse Effects The main toxicity of 5-fluorouracil is bone marrow suppression.

Important Concept

The adverse effect profile of cisplatin and carboplatin resembles that of the aminoglycoside antibiotics.

2.2 Alkylating Agents

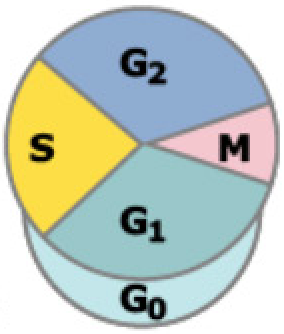
The alkylating agents are cell-cycle nonspecific drugs that covalently alter DNA bases, leading to DNA damage by *cross-linking, abnormal base pairing,* and DNA strand breakage. The alkylating agents have organ-specific toxicities.


T
A
G
C
G
C
A
T
G
C
C
G
Sugar-phosphate backbone
Bifunctional alkylating agents can cause intrastrand linking and cross-linking

▲**Figure 6-2.2A** Bifunctional Alkylating Agents

G2 phase
- Bleomycin

S phase specific
- Cytarabine
- 6-Mercaptopurine
- 6-Thioguanine
- 5-Flouriouracil
- Methotrexate
- Hydroxyurea
- Irinotecan (blocks topoisomerase I)
- Etoposide (blocks topoisomerase II)



M phase
- Vinblastine } Blocks tubular polymerization
- Vincristine } Blocks tubular polymerization
- Paclitaxel }-Blocks depolymerization of microtubules

M phase: Cell growth stops at this stage; cellular energy is focused on the orderly division into two daughter cells. **Mitotic inhibitors work here.**

S phase: DNA replication. **DNA synthesis inhibitors work in this phase.**

G_0 phase
- Alkylating agents (cyclophosphamide, cisplatin, procarbazine)
- Antitumor antibiotics (doxorubicin, daunorubicin)
- Nitrosoureas (Lomustine, carmustine)
- Cisplatin

▲**Figure 6-2.2B** Cell-Cycle Specificity of Anticancer Drugs

2.2.1 Cisplatin and Carboplatin

Cisplatin and carboplatin are *platinum-containing drugs* used to treat testicular, bladder, lung, and ovarian cancers. For testicular cancers, cisplatin is very effective in treating non-seminoma germ cell tumors. This contrasts with seminomas that are sensitive to radiation therapy.

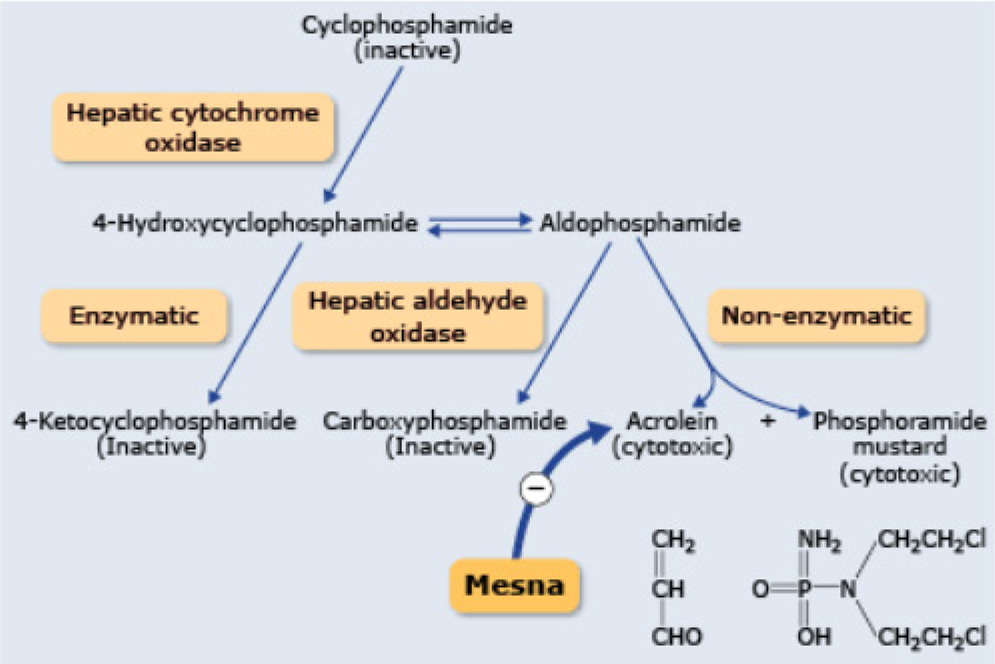
Mechanism of Action Cisplatin and carboplatin *covalently link to DNA, primarily at guanine nucleotides*. This leads to DNA cross-linking and damage.

Adverse Effects The primary adverse effects of cisplatin and carboplatin are *nephrotoxicity* and *ototoxicity* (potentially leading to deafness). The risk of nephrotoxicity is lessened by maintaining adequate hydration during infusions.

2.2.2 Cyclophosphamide

Cyclophosphamide is an alkylating agent that is activated by cytochrome *P450 enzymes*. Used for treatment of breast and ovarian cancers, as well as non-Hodgkin lymphoma, cyclophosphamide is also used to treat some autoimmune disorders such as *systemic lupus erythematosus* and *rheumatoid arthritis*.

Mechanism of Action
Cyclophosphamide is metabolized to phosphoramide mustard compounds that covalently bind to DNA, mainly at guanines, leading to cross-linking and DNA damage.


Cyclophosphamide (inactive)
Hepatic cytochrome oxidase
4-Hydroxycyclophosphamide
Aldophosphamide
Enzymatic
Hepatic aldehyde oxidase
Non-enzymatic
4-Ketocyclophosphamide (Inactive)
Carboxyphosphamide (Inactive)
Acrolein (cytotoxic)
+
Phosphoramide mustard (cytotoxic)
Mesna
CH_2
CH
CHO
NH_2
O=P—N
OH
CH_2CH_2Cl
CH_2CH_2Cl

▲**Figure 6-2.2C** Cyclophosphamide: Mechanism of Action

Adverse Effects The most common adverse effect is *bone marrow suppression*. The metabolism of cyclophosphamide also leads to generation of a reactive metabolite *acrolein*. This can damage the lining of the bladder, leading to *hemorrhagic cystitis,* a condition that can present as gross blood in the urine. The toxicity of acrolein is lessened by coadministration of cyclophosphamide with *MESNA* (2-mercaptoethanesulfonate), a compound that traps and detoxifies acrolein.

2.3 Plant Alkaloids

The plant alkaloids include vinblastine, vincristine, paclitaxel, and etoposide. The first three drugs target the mitosis (M) phase of the cell cycle. Etoposide inhibits DNA synthesis.

2.3.1 Vinblastine and Vincristine

Vinblastine and vincristine are used for treatment of acute leukemias, lymphomas, and neuroblastoma.

Mechanism of Action Vinblastine and vincristine *block mitotic spindle formation* in the M phase by *binding tubulin* and preventing polymerization. This arrests cells in metaphase.

Adverse Effects The main adverse effect of these agents is *peripheral neuropathy*.

2.3.2 Paclitaxel

Paclitaxel is used for treatment of advanced breast and ovarian cancer.

Mechanism of Action Paclitaxel interferes with mitotic spindle by preventing disassembly of *microtubules* into tubulin monomers.

Adverse Effects Paclitaxel can cause *neurotoxicity* and bone marrow suppression.

2.3.3 Etoposide

Etoposide is used for treatment of small cell lung cancer and testicular cancer.

Mechanism of Action Etoposide is a *topoisomerase II inhibitor* that *blocks DNA unwinding*. This interferes with the S phase of cell cycle.

Adverse Effects The main adverse effect of etoposide is bone marrow suppression.

2.4 Antibiotics

Several cancer chemotherapy agents are derived from natural antibiotics.

2.4.1 Bleomycin

Bleomycin is a mixture of glycopeptides used to treat Hodgkin lymphoma, squamous cell carcinomas, and testicular carcinoma.

Mechanism of Action Bleomycin's exact mechanism of action is not understood, but it is known to *cause DNA damage* and to disrupt the G2 phase of the cell cycle.

Important Concept

Few drugs cause pulmonary fibrosis (amiodarone, in addition to bleomycin). Watch for boards questions that refer to progressive shortness of breath or chest x-ray showing nonspecific abnormalities.

Adverse Effects Bleomycin's most worrisome adverse effect is *pulmonary fibrosis,* which can be irreversible. Other side effects include dermatographism (raised skin when scratched or injured), hyperpigmentation, and *Raynaud phenomenon*.

2.4.2 Doxorubicin and Daunorubicin

Doxorubicin and daunorubicin are anthracycline antibiotics used to treat leukemias, Hodgkin lymphoma, and a variety of solid tumors.

Important Concept

Dilated cardiomyopathy caused by doxorubicin and daunorubicin is a usually irreversible effect that can result in heart failure.

Mechanism of Action Doxorubicin and daunorubicin intercalate into DNA, altering its structure, replication, and topoisomerase II function. Like alkylating agents (such as cisplatin), these drugs are cell cycle nonspecific.

Adverse Effects The most serious adverse effect from doxorubicin or daunorubicin is *dilated cardiomyopathy,* with potentially life-threatening consequences. Prior to starting doxorubicin or daunorubicin therapy, patients should have thorough cardiac evaluation (echocardiography). Patients with preexisting cardiac problems should usually not be treated with doxorubicin or daunorubicin.

These agents also can produce damage and discoloration of nails (sometimes in "rings" associated with rounds of chemotherapy) and *reddish discoloration of urine*.

2.4.3 Actinomycin D (Dactinomycin)

Actinomycin D is an anthracycline antibiotic used to treat Ewing sarcoma, pediatric rhabdomyosarcoma, and Wilms tumor. Ewing sarcoma and rhabdomyosarcoma are *aggressive tumors* that are quite difficult to treat if presenting as metastatic disease.

Important Concept

Actinomycin D is high yield for boards because it is used to treat cancers with few other treatment options.

Mechanism of Action Actinomycin D *inhibits RNA polymerase*.

Adverse Effects The main adverse effect of actinomycin D is bone marrow suppression.

2.5 Hormone Therapy

Some cancer therapies target nuclear hormone receptors such as the glucocorticoid, estrogen, and androgen receptors. The goal of therapy can be to block receptor function or to influence differentiation of the tumor cells.

2.5.1 Glucocorticoids

Glucocorticoids, such as prednisone, have *inhibitory effects on lymphocytes* and are used in the treatment of lymphomas and acute leukemias.

2.5.2 Estrogen Receptor Blockers (Tamoxifen)

Estrogen receptor antagonists are used in the treatment of *estrogen-dependent cancer,* including some types of *breast cancer* (discussed more fully in endocrine pharmacology in chapter 9). The prototype drug is *tamoxifen,* a full antagonist of estrogen receptors in all tissues. Such drugs should be used only for estrogen receptor-positive cancers. The side effects associated with estrogen receptor blockers resemble those of menopause, including *hot flashes*.

2.5.3 Aromatase Inhibitors

Aromatase inhibitors block an enzyme needed for the synthesis of estrogens. These drugs limit estrogen production and are used in the treatment of estrogen receptor–positive breast cancers.

Exemestane The prototype aromatase inhibitor, exemestane is an *irreversible antagonist* used in treatment of breast cancer.

Anastrozole and Letrozole These *reversible aromatase inhibitors* are used in treatment of estrogen receptor-positive breast cancers. They are also used illicitly in athletes abusing anabolic steroids to prevent conversion of the anabolic drugs to estrogens, thereby preventing gynecomastia and other unwanted estrogen-related effects.

2.5.4 Prostate Cancer Therapies

Prostate cancers are often responsive to the action of androgens, especially dihydrotestosterone. Consequently, androgen receptor antagonists are used to treat prostate carcinoma. The prototype drug is flutamide, with bicalutamide, a newer drug, having fewer side effects. These drugs are often given with leuprolide, a gonadotropin-releasing hormone (GnRH) agonist used to prevent reflex increase in luteinizing hormone that would otherwise result from antiandrogen receptor therapy.

2.5.5 All-trans Retinoic Acid (ATRA)

ATRA is used for the treatment of *acute promyelocytic leukemia* (APL), the M3 subtype of acute myelogenous leukemia (AML). APL involves rearrangement of the retinoic acid receptor by the t(15;17) translocation. The promyelocytes in APL release a variety of products that can lead to excessive coagulation and bleeding, potentially leading to *disseminated vascular coagulation* (DIC). ATRA acts on the retinoic acid receptor and promotes differentiation and reduced toxicity of the immature myeloid cells, reducing the risk of coagulopathy.

Clinical Application

In a patient presenting with acute leukemia, ruling in or ruling out APL is a critical first step. Failure to recognize APL can lead to patient death due to coagulopathy. Early diagnosis leads to prompt therapy, including use of the targeted therapy ATRA, a drug that would be ineffective in any other acute leukemia.

2.6 Immunotherapy

A number of the more recently developed anticancer drugs are antibodies or other agents directed against specific cancer targets. In some cases, these drugs are also used for their immunosuppressive effects in the treatment of autoimmune diseases.

2.6.1 Rituximab (Rituxan, Anti-CD20)

Rituximab is a chimeric monoclonal antibody used to treat B cell lymphomas and leukemias. Rituximab is also approved for treatment of severe *rheumatoid arthritis* and is used off-label for preventing *transplant organ rejection*.

Mechanism of Action Rituximab targets the CD20 protein found in B-lymphocytes. Rituximab is used for B cell related malignancies as well as treatment of autoimmune disease.

Adverse Effects As a foreign protein, rituximab can cause infusion reactions. Rituximab also can cause complications due to immune suppression, including reactivation of hepatitis B and other viruses. A rare adverse effect is *progressive multifocal leukoencephalopathy* (PML), an often fatal disease caused by activation of the JC virus.

2.6.2 Trastuzumab (Herceptin)

Trastuzumab is a humanized monoclonal antibody used to treat breast cancers that over-express the HER2 protein.

Mechanism of Action Trastuzumab *inhibits the HER2/neu receptor involved in tumor cell proliferation*. In the pathology workup of breast cancer, determination of HER2 expression status is key in determining whether trastuzumab is a therapeutic option.

Adverse Effects The major adverse effect of trastuzumab is on the heart. Up to 7% of patients experience *cardiac dysfunction*. As a result, regular cardiac screening during trastuzumab treatment is important. Another limitation of trastuzumab is its *high cost* (up to $100,000/year), and some health insurance plans refuse to cover payment.

2.6.3 Bevacizumab (Avastin)

Bevacizumab is a humanized monoclonal antibody that *inhibits angiogenesis* (growth of new blood vessels). It is used to treat a variety of cancers, including colorectal, lung, kidney, ovarian, and glioblastoma. Bevacizumab also recently gained approval for treatment of *macular degeneration* using intraocular injection. Bevacizumab received significant media coverage after the FDA withdrew it as a treatment option for breast cancer.

Mechanism of Action Bevacizumab is a monoclonal antibody that *blocks vascular endothelial growth factor A (VEGF-A)*.

Adverse Effects The major adverse effects are hypertension and increased risk of bleeding. Unusual *perforations of the bowel* and nasal septum have been reported. These side effects are not seen with the intraocular injection used for treatment of macular degeneration. As with trastuzumab, the high cost of bevacizumab is an issue, as many health insurance companies refuse to pay for therapy.

2.6.4 Alemtuzumab (Campath)

Alemtuzumab is a humanized monoclonal antibody that targets mature lymphocytes. Alemtuzumab is used in the treatment of chronic lymphocytic leukemia and T cell lymphomas. It also showed effectiveness in treatment of *multiple sclerosis*. Alemtuzumab was withdrawn from the U.S. market as a treatment option for leukemia in August 2012 but is expected to be relaunched with an approval for multiple sclerosis treatment.

Mechanism of Action Alemtuzumab binds to *CD52,* a protein present on the surface of mature lymphocytes. Cells bound to alemtuzumab are targeted for destruction.

Adverse Effects Alemtuzumab has been associated with infusion-related events, including shortness of breath, hypotension, rigors, and fever.

2.6.5 Cetuximab (Erbitux)

Cetuximab is a humanized monoclonal antibody that targets the *epidermal growth factor receptor (EGFR)*. Cetuximab is used in the treatment of metastatic colorectal, head, and neck cancers.

Mechanism of Action Cetuximab is a mouse/human chimeric monoclonal antibody that targets the ligand-binding domain of the EGFR, and inhibits receptor phosphorylation and downstream events.

Adverse Effects Cetuximab has been associated with infusion-related events, including shortness of breath, hypotension, rigors, and fever.

2.6.6 Imatinib (Gleevec) and Related Drugs

Imatinib is a chemotherapy drug used to treat chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GISTs). Imatinib represented a *substantial breakthrough in the treatment of CML,* which previously was difficult to treat. Prior to the approval of imatinib, the best chemotherapy options for CML were interferons, which often did not induce remission and had many unpleasant side effects.

Mechanism of Action Imatinib *inhibits a specific tyrosine kinase* found in CML and GISTs. In CML, a translocation t(9;22) ("Philadelphia chromosome") causes constitutive activation of the ABL tyrosine kinase.

Adverse Effects Imatinib is generally well tolerated, allowing for chronic therapy. The most common adverse effects are cytopenias and weight gain.

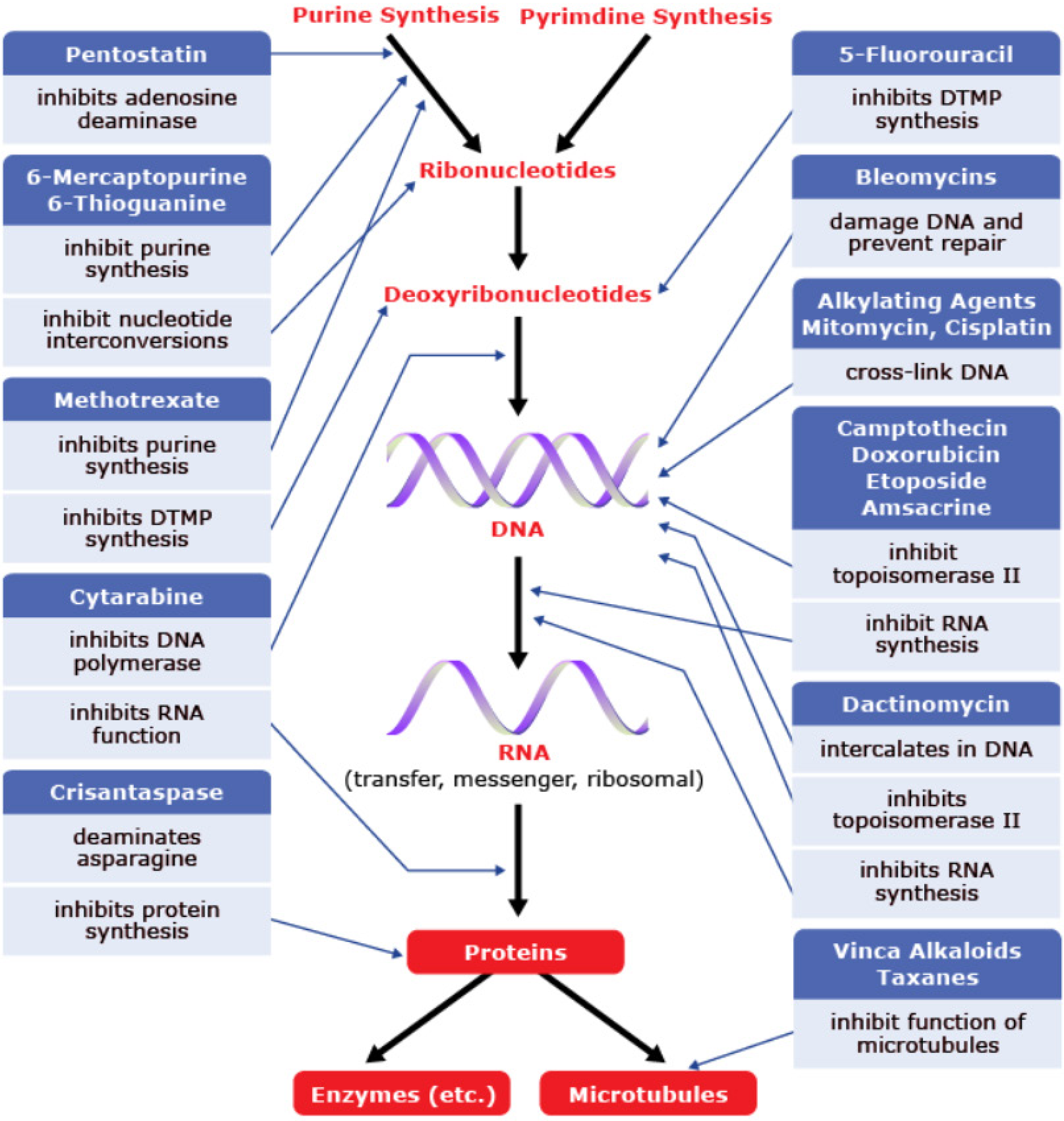
Related Tyrosine Kinase Inhibitors Over time, tumor cells can become resistant to imatinib by mutations in the BCR-ABL protein. As a result, several second-generation tyrosine kinase inhibitors have been marketed, including dasatinib and nilotinib. Dasatinib has been associated with cytopenias and pleural effusions. Nilotinib has an FDA black box warning due to *prolongation of the QT interval,* which carries risk for *fatal arrhythmias*.

2.7 Asparaginase

Asparaginase is an unusual chemotherapy drug used to treat acute lymphoblastic leukemia (ALL) and mast cell tumors.

Mechanism of Action Asparaginase catalyzes the hydrolysis of asparagines to aspartic acid. Most normal cells are able to synthesize their own asparagines (thus, the classification of asparagine as a nonessential amino acid). However, tumor cells in ALL and some other cancers are unable to synthesize their own asparagine in sufficient quantities and depend on circulating asparagine. Treatment with *asparaginase depletes circulating asparagines,* leading to tumor cell death.

Adverse Effects Asparaginase is associated with *pancreatitis* as well as allergic or hypersensitivity reactions. Asparaginase can also cause *bleeding or thrombotic complications* by interfering with protein synthesis of natural clotting (as in fibrinogen) and anticlotting (as in antithrombin III) factors.


Purine Synthesis
Pyrimdine Synthesis
Pentostatin
inhibits adenosine deaminase
6-Mercaptopurine
6-Thioguanine
inhibit purine synthesis
inhibit nucleotide interconversions
Methotrexate
inhibits purine synthesis
inhibits DTMP synthesis
Cytarabine
inhibits DNA polymerase
inhibits RNA function
Crisantaspase
deaminates asparagine
inhibits protein synthesis
Ribonucleotides
Deoxyribonucleotides
DNA
RNA
(transfer, messenger, ribosomal)
Proteins
Enzymes (etc.)
Microtubules
5-Fluorouracil
inhibits DTMP synthesis
Bleomycins
damage DNA and prevent repair
Alkylating Agents
Mitomycin, Cisplatin
cross-link DNA
Camptothecin
Doxorubicin
Etoposide
Amsacrine
inhibit topoisomerase II
inhibit RNA synthesis
Dactinomycin
intercalates in DNA
inhibits topoisomerase II
inhibits RNA synthesis
Vinca Alkaloids
Taxanes
inhibit function of microtubules

▲**Figure 6-2.7** Cytotoxic Agents: Sites of Action

3 Immunosuppressants (Anti-Rejection Drugs)

Immunosuppressants are used to prevent rejection of transplanted organs as well as for treatment of autoimmune diseases such as rheumatoid arthritis and psoriasis.

3.1 Overview of Immunosuppressant Drugs

The prototype anti-rejection drugs are *cyclosporine* and *tacrolimus*. Other agents include sirolimus and mycophenolic acid.

3.2 Cyclosporine

Cyclosporine was the first widely used drug to prevent organ transplant rejection. More recently, cyclosporine has been used to treat autoimmune diseases. Cyclosporine as an ophthalmic solution is used to treat dry eyes.

Mechanism of Action Cyclosporine inhibits calcineurin, a protein that regulates interleukin-2 and other cytokines. This prevents T cell activation.

Pharmacokinetics Cyclosporine is predominantly metabolized by cytochrome P450 (CYP) 3A4. Inhibitors of this enzyme (azoles, erythromycin, grapefruit juice) can lead to toxic levels of cyclosporine. Conversely, inducers of CYP3A4 (carbamazepine, phenobarbital, phenytoin, St. John's wort) reduce cyclosporine levels. Careful monitoring of cyclosporine blood concentrations, with proper dose adjustments when CYP inhibitors or inducers are coadministered, is essential.

Important Concept

For boards questions involving cyclosporine therapies, remember that inhibitors of CYP3A4 prevent the metabolism of cyclosporine, while inducers of the same enzyme reduce its level.

Adverse Effect The main dose-limiting adverse effect is *nephrotoxicity,* which can become evident as a rising serum creatinine value. When cyclosporine is used in a renal transplant recipient, it can be difficult to determine whether an increasing creatinine value is due to drug toxicity or allograft rejection. Other adverse effects of cyclosporine include *neuropathy* and *gingival hyperplasia* (an unusual side effect also seen with phenytoin).

3.3 Tacrolimus

Tacrolimus has a mechanism of action and toxicity profile that is very similar to cyclosporine. However, tacrolimus has shown more favorable long-term outcomes in *preventing allograft rejection* compared to cyclosporine, and has thus become more widely used. Tacrolimus is also used for treatment of *autoimmune disease,* such as ulcerative colitis.

3.4 Sirolimus (Rapamycin)

Sirolimus is an anti-rejection drug that is used most commonly in kidney transplant recipients. The main advantage of sirolimus compared to cyclosporine and tacrolimus is low renal toxicity. Sirolimus has also been used as a *coating on cardiac stents* to prevent restenosis following balloon angioplasty.

Mechanism of Action Unlike cyclosporine and tacrolimus, sirolimus does not inhibit calcineurin, but instead *inhibits the mTOR (mammalian target of rapamycin)* complex involved in the cellular response to interleukin-2.

Adverse Effects The most serious adverse effect of sirolimus therapy is *interstitial pneumonitis,* particularly in lung transplant recipients. Although sirolimus has less nephrotoxicity compared to cyclosporine and tacrolimus, long-term therapy can result in renal damage. Sirolimus has a long half-life (~60 hrs.).

3.5 Everolimus

Everolimus is a derivative of sirolimus also used to prevent allograft rejection. Everolimus also is approved for treatment of advanced kidney cancer, astrocytoma, and certain neuroendocrine tumors.

3.6 Mycophenolate Mofetil

Mycophenolate is an immunosuppressant used for prevention of allograft rejection and for treatment of *autoimmune diseases* (Behçet disease, lupus erythematosus). Mycophenolate may be used in conjunction with other anti-rejection drugs.

Mechanism of Action Mycophenolate *inhibits inosine monophosphate dehydrogenase,* an enzyme in the synthesis pathway for purines, especially guanine. This pathway is particularly critical for the growth of B and T lymphocytes, which are unable to use a separate scavenger pathway for purine synthesis.

Adverse Effects Mycophenolate is a potent immunosuppressant due to suppression of B and T lymphocytes. *Opportunistic infections* and cytopenias are the most common serious adverse effects.

CHAPTER 7 Pulmonary Pharmacology

1 Therapies for Asthma

Asthma treatment has changed over the years with the recognition that asthma is fundamentally an *inflammatory disease,* with symptoms such as *bronchoconstriction* (wheezing, difficulty breathing) and *increased airway mucus*.

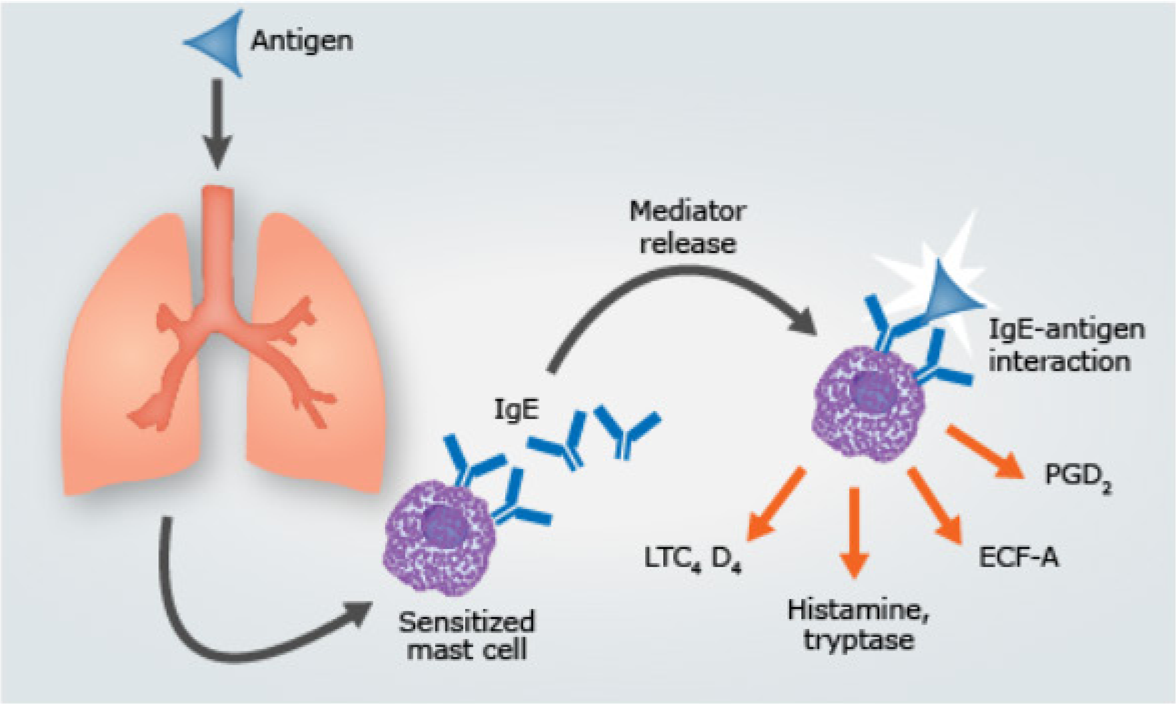
There are seven main categories of drugs for asthma therapy:

1. Corticosteroids
2. β2-adrenergic receptor agonists
3. Muscarinic receptor blockers
4. Theophylline
5. Cromolyn sodium
6. Leukotriene antagonists
7. Antibodies against IgE (omalizumab)

Corticosteroids and agonists at β2-adrenergic receptors are currently the most widely used medications for asthma.

1.1 Overview of Asthma

The inflammatory process in asthma leads to a variety of problems. The airway epithelium becomes infiltrated by immune cells, and mucus production increases.

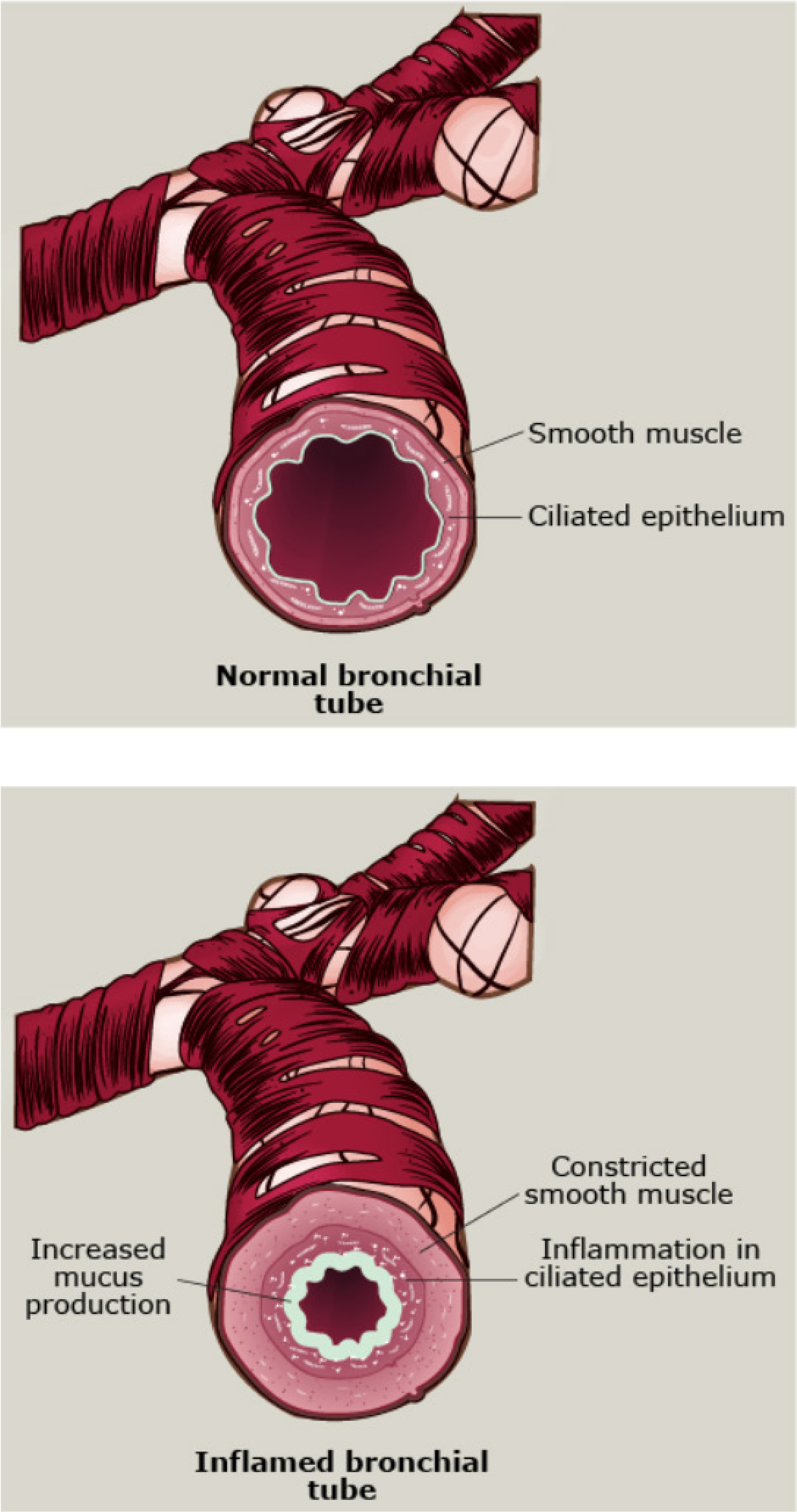


▲**Figure 7–1.1A** Pathogenesis of Asthma

USMLE® Key Concepts

For Step 1, you must be able to:

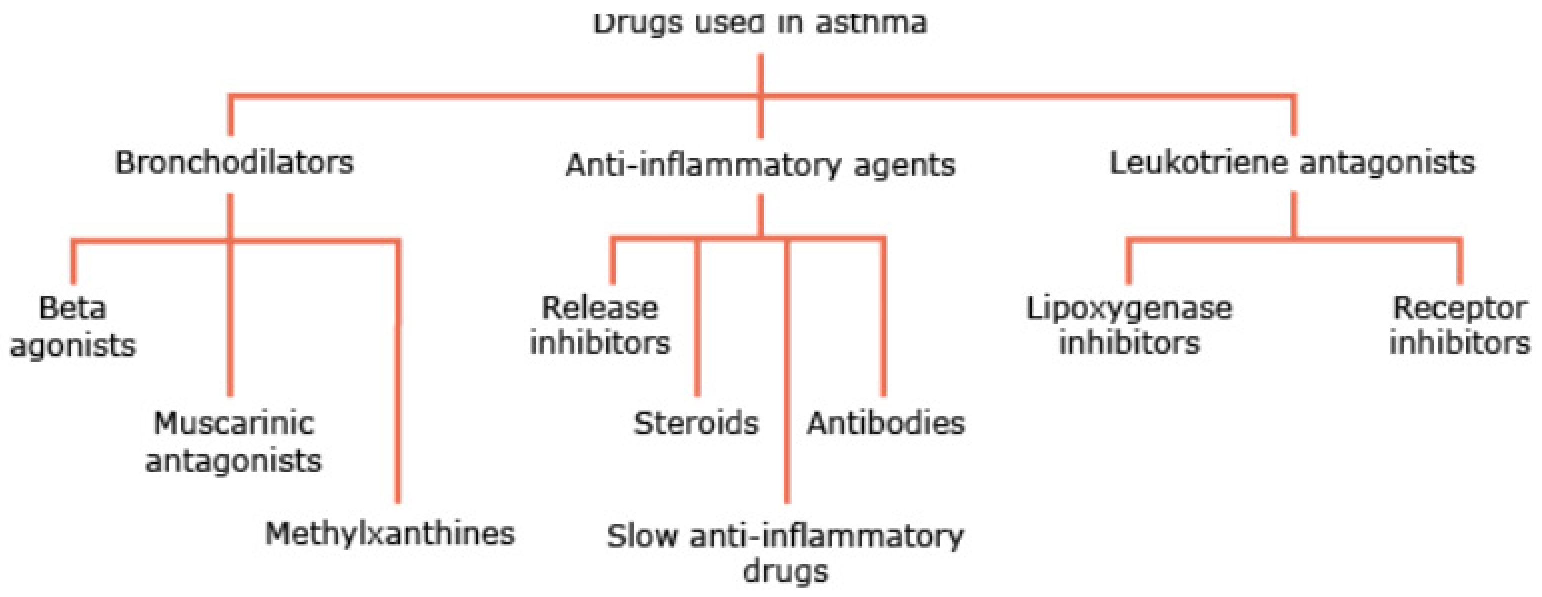
- Describe the major classes of drugs used in asthma and their mechanism of action and adverse effects.
- Explain the therapeutic approaches for acute versus chronic management of asthma.
- Identify therapies appropriate for the three stages of chronic obstructive pulmonary disease.


Smooth muscle
Ciliated epithelium
Normal bronchial tube
Constricted smooth muscle
Increased mucus production
Inflammation in ciliated epithelium
Inflamed bronchial tube

▲**Figure 7–1.1B** Normal vs. Inflamed Lung Tissue

1.2 Treatment Goals in Asthma Therapy

The long-term goal in asthma therapy is to treat the underlying inflammatory process. Acute symptoms are treated as needed.


Drugs used in asthma
Bronchodilators
Anti-inflammatory agents
Leukotriene antagonists
Beta agonists
Muscarinic antagonists
Methylxanthines
Release inhibitors
Steroids
Antibodies
Slow anti-inflammatory drugs
Lipoxygenase inhibitors
Receptor inhibitors

▲ **Figure 7–1.2** Asthma Drugs

1.3 Corticosteroids

Corticosteroids are the cornerstone of *chronic treatment* for moderate to severe asthma. To avoid adverse systemic effects, *inhaled corticosteroids* are used instead of systemic (oral) steroids whenever possible. Corticosteroids work by inhibiting white blood cells and preventing cellular infiltration and release of inflammatory mediators such as interleukins and TNF-α.

1.3.1 Inhaled Corticosteroids

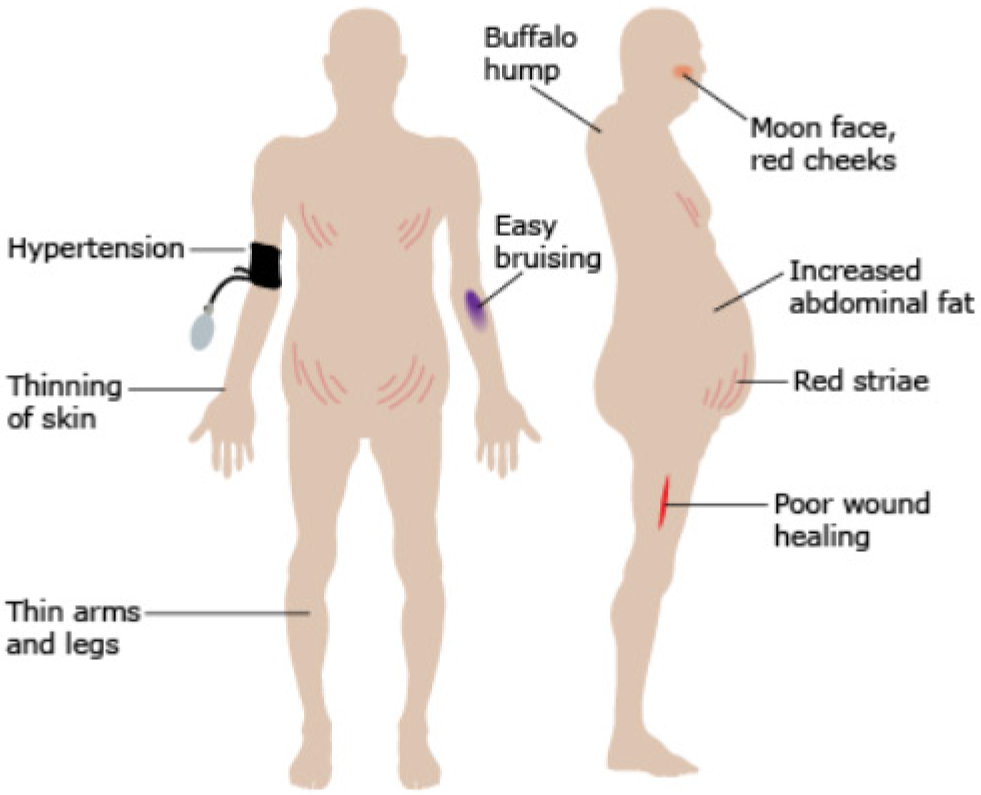
Inhaled corticosteroids have minimal systemic side effects but, when used properly, target the inflammatory process in the lungs. Inhaled agents used clinically include budesonide, beclomethasone, fluticasone, and mometasone. Fluticasone and mometasone have the fewest systemic effects. Inhaled corticosteroids are indicated for chronic treatment of moderate to severe asthma, with severity defined by factors such as frequency of symptoms, visits to emergency room, etc.

The inhaled corticosteroids have relatively few adverse effects, most of which are related to local immunosuppression, as in oropharyngeal candiasis.

1.3.2 Systemic Corticosteroids

Systemic corticosteroids are used for more *severe asthma* when inhaled agents are insufficient. The most common agents are prednisone (oral) and prednisolone (intravenous).

Systemic corticosteroids carry the well-known *cushingoid risks,* including delayed wound healing, osteoporosis, alteration of fat distribution, and glucose intolerance. When possible, therapy with systemic corticosteroids is limited to the shortest duration that brings the asthma symptoms under control.



▲**Figure 7–1.3** Cushingoid Side Effects of Corticosteroids

1.4 β2-Adrenergic Agonists

β2-adrenergic agonists are used to treat *acute bronchoconstriction* and for *prophylaxis of exercise-induced asthma*. Binding of the β2-adrenergic receptor in bronchial smooth muscle activates adenylate cyclase, increases cAMP, and causes bronchodilation.

1.4.1 β1/β2 Nonselective

Albuterol (salbutamol) and terbutaline are two short-acting β2-adrenergic agonists that also activate the β1-adrenergic receptors.

- **Clinical Indications:** Inhaled albuterol is often used for *acute treatment* of bronchoconstriction. In more severe asthma attacks, albuterol may be given by *nebulizer* (aerosol vapor).
- **Adverse Effects:** The adverse effects of albuterol and terbutaline are mostly related to activation of the β1-adrenergic receptor, producing cardiac side effects such as *tachycardia*.

1.4.2 β2 Selective Agents

Salmeterol and formoterol are long-acting agents that are very selective toward β2-adrenergic receptors, with minimal effects on β1-adrenergic receptors.

- **Clinical Indications:** Long-acting inhaled β2-adrenergic receptor agonists are used for *chronic management* of moderate to severe asthma, often in combination with a corticosteroid. They are *not* appropriate for management of acute asthma symptoms.
- **Adverse Effects:** Large-scale retrospective analyses have raised safety concerns with the *long-acting β2-adrenergic agonists,* particularly an increase in the *risk of death due to asthma crisis*. The mechanism is not entirely clear, because the majority of patients respond favorably to these drugs.

1.5 Muscarinic Receptor Antagonists

Muscarinic receptor antagonists are a second-line therapy for asthma. The two most commonly used agents are *ipratropium* (short-acting) and *tiotropium* (long-acting). As inhaled agents, the side effects are usually minimal but may include atropine-like effects.

Memory Aid

You can recognize antimuscarinic drugs because they often have "trop" in their names: a**trop**ine, ipra**trop**iium, and tio**trop**ium.

1.6 Theophylline

Theophylline is a methylxanthine compound chemically related to caffeine. Once a mainstay of asthma therapy, theophylline is now a second-line drug. Theophylline and caffeine are both used to treat apnea associated with prematurity.

Mechanism of Action Theophylline has two main mechanisms of action: inhibition of *phosphodiesterase* (increased cAMP) and antagonism of the bronchoconstrictive transmitter *adenosine*. Aminophylline is an intravenous form of theophylline used for severe asthma attacks.

Adverse Effects Theophylline has a *narrow therapeutic window* and can cause adverse effects such as nausea, diarrhea, cardiac arrhythmias, and central nervous system excitation. Theophylline plasma concentrations are often monitored to help patients avoid toxic side effects.

1.7 Cromolyn Sodium and Nedocromil

Cromolyn sodium and nedocromil are seldom-used asthma drugs that work by *preventing degranulation of mast cells*. This decreases release of bronchoconstrictive compounds like histamine and leukotrienes. Cromolyn sodium and nedocromil have narrow clinical utility and are used mainly as prophylaxis for known asthma triggers, such as pets and cold air.

1.8 Antagonists to the Leukotriene System

The leukotrienes include compounds with bronchoconstrictive effects. Several drugs on the market target the leukotriene system.

1.8.1 Montelukast and Zafirlukast

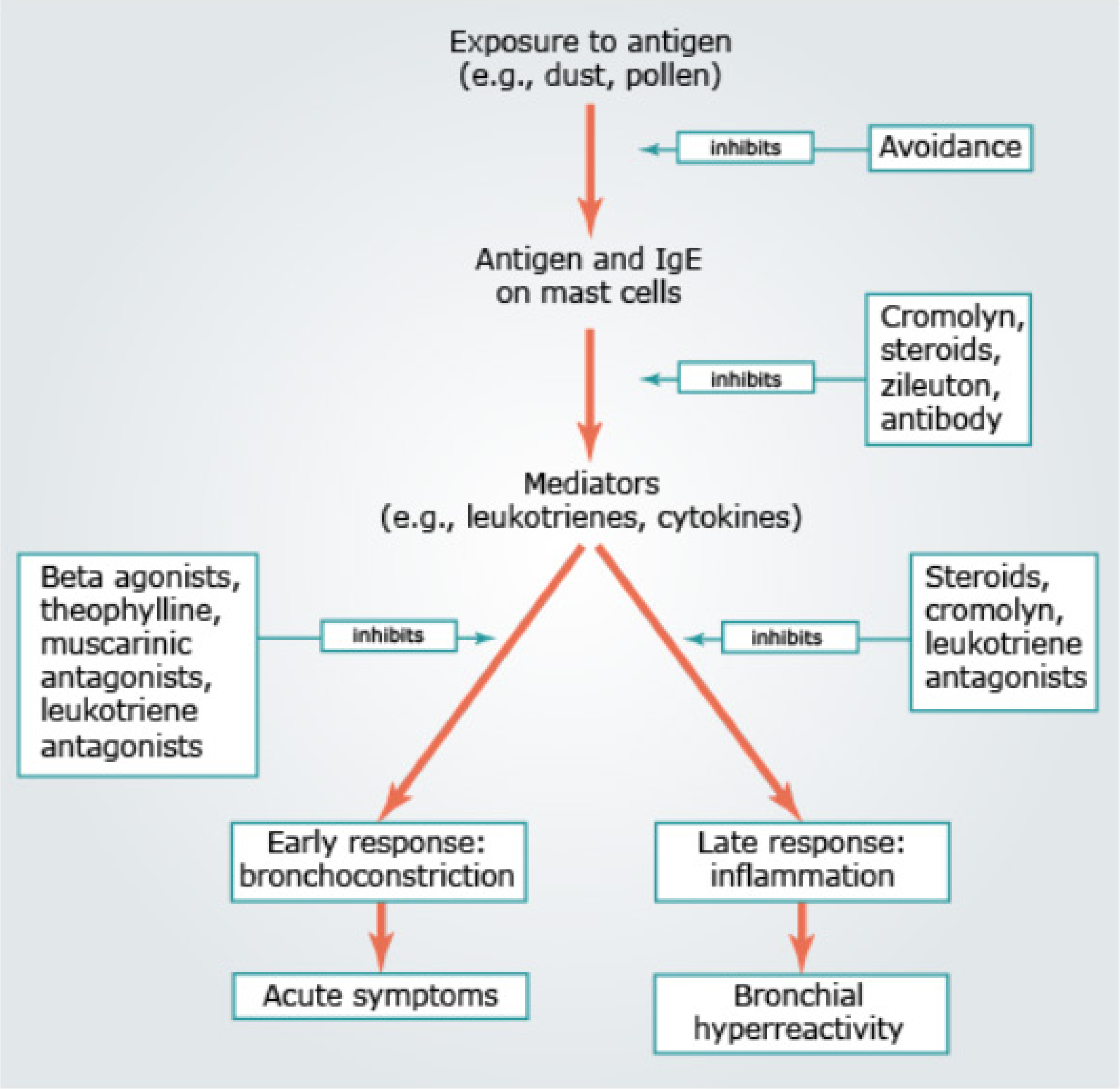
Montelukast and zafirlukast (the "lukasts") block leukotriene receptors. These drugs are given orally but produce clinical effect in only about one third of patients. The side-effect profile is generally good, but there is an association with the *Churg-Strauss syndrome: autoimmune vasculitis* affecting the lung and other organs.

1.8.2 Zileuton

Zileuton is an *inhibitor of 5-lipoxygenase,* the key enzyme in the conversion of arachidonic acid to leukotrienes. Zileuton is very effective for preventing exacerbation of asthma by aspirin. Zileuton is not commonly used.

1.9 Omalizumab (Xolair)

Omalizumab is a humanized *monoclonal antibody to IgE*. This prevents IgE from binding allergen and thereby activating mast cells. Omalizumab is very expensive (> $10,000/year) and must be given parenterally. Omalizumab is reserved for treatment of asthma not responsive to other less expensive therapies.


Exposure to antigen
(e.g., dust, pollen)
inhibits
Avoidance
Antigen and IgE
on mast cells
Cromolyn,
steroids,
zileuton,
antibody
inhibits
Mediators
(e.g., leukotrienes, cytokines)
Beta agonists,
theophylline,
muscarinic
antagonists,
leukotriene
antagonists
inhibits
Steroids,
cromolyn,
leukotriene
antagonists
inhibits
Early response:
bronchoconstriction
Late response:
inflammation
Acute symptoms
Bronchial
hyperreactivity

▲**Figure 7–1.9** Asthma Treatment Strategies

2 Therapies for Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a *progressive, irreversible disease* characterized by *airflow obstruction*. Cigarette smoking is the strongest risk factor for COPD, and smoking cessation is a high priority for COPD patients. Forced expiratory volume in one second *(FEV_1)* is the respiratory function typically followed in COPD. FEV_1 declines with greater severity of COPD.

2.1 Overview of COPD Therapies

Medications for COPD in general have limited effectiveness, but can improve symptoms by increasing airflow and decreasing disease exacerbations. The first-line drugs for COPD are muscarinic receptor antagonists and β2-adrenergic receptor agonists. Inhaled corticosteroids are used in more severe disease.

2.2 Stage-Based Treatment

Therapy for COPD is guided by the stage of disease.

2.2.1 Mild COPD

Mild (stage I) COPD is characterized by FEV_1 of 80% or greater. The typical therapy is *short-acting bronchodilator* (ipratropium or albuterol) when needed.

2.2.2 Moderate COPD

Moderate (stage II) COPD is characterized by FEV_1 of 50% to 80%. The recommended therapy is a *long-acting bronchodilator* (tiotropium or salmeterol) and an inhaled corticosteroid.

2.2.3 Severe COPD

Severe (stage III) COPD is characterized by FEV_1 of less than 50%. The recommended therapies are those used in stage II *(long-acting bronchodilator* and *inhaled corticosteroid)* with antibiotics and supplemental oxygen used as needed.

▼**Table 7–2.2** Treatment of COPD

Stage	Characteristics	Long-Term Control
I: Mild COPD	FEV_1 greater than 80% predicted	Short-acting bronchodilator when needed.
II: Moderate COPD	FEV_1 50% to 80% predicted	Regular treatment with one or more bronchodilators. Inhaled glucocorticosteroid.
III: Severe COPD	FEV_1 less than 50% predicted	Regular treatment with one or more bronchodilators. Inhaled glucocorticosteroid. Antibiotics for acute exacerbations of COPD characterized by increased volume and purulence of secretions. Long-term oxygen therapy.

3 Therapies for Allergic Rhinitis

Rhinitis is inflammation of the mucous membranes of the nose with symptoms of itchiness, rhinorrhea, sneezing, and nasal congestion. Typical triggers for attacks include a variety of *allergens* (animal dander, dust, pollen) that interact with *mast cells coated with IgE*. Rhinitis symptoms are produced by the inflammatory mediators (such as *histamine* or *leukotriene*) released by the mast cells.

3.1 Overview of Therapies for Allergic Rhinitis

Oral antihistamines and decongestants (often in combination products) are first-line therapies. Intranasal corticosteroids are used for patients with more prolonged symptoms.

3.2 Antihistamines

Antihistamines are the most frequently used medications in the treatment of allergic rhinitis. The *first-generation antihistamines* (diphenhydramine and chlorpheniramine) penetrate the central nervous system and are associated with sedation and other side effects (dry mouth and difficulty urinating). The *second-generation antihistamines* (fexofenadine and loratadine) are often referred to as "non-drowsy" and are much less likely to produce sedating effects.

3.3 α-Adrenergic Agonists

α-adrenergic agonists, such as *phenylephrine* and *oxymetazoline,* are used as *nasal sprays* in the treatment of allergic rhinitis and act by constricting dilated arterioles in the nasal mucosa. These drugs should not be used for extended periods and are associated with rebound nasal congestion if used for more than several days consecutively.

3.4 Corticosteroids

Corticosteroids such as *beclomethasone, fluticasone,* and *triamcinolone* are effective as nasal sprays in the treatment of allergic rhinitis.

The systemic absorption of intranasal corticosteroids is minimal. Patients should avoid deep inhalation when using the nasal spray. Local irritation of the nasal mucosa may occur.

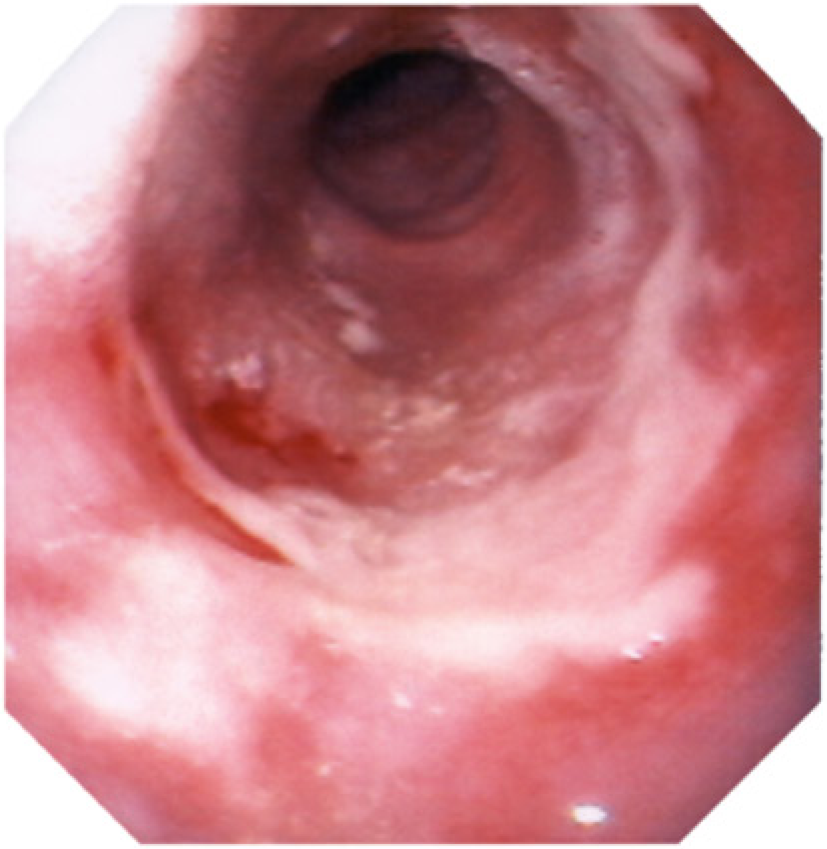
CHAPTER 8 Drugs Affecting the Gastrointestinal System

1 Therapies for Gastroesophageal Reflux and Peptic Ulcer Disease

Gastroesophageal reflux and peptic ulcers are common disorders. In some cases, symptoms are mild and require only therapies to reduce stomach acid production or neutralize gastric pH. In other cases, more aggressive therapy is needed to manage disease and prevent long-term complications such as Barrett esophagus and esophageal cancer.

The major treatments for gastroesophageal reflux disease (GERD) and peptic ulcer disease are:

- Histamine-2 antagonists
- Proton pump antagonists
- Antacids
- Physical protectors of gastric mucosa
- Prostaglandin analogs



David M. Martin, M.D./Science Source

▲**Figure 8–1.0** Barrett Esophagus

USMLE® Key Concepts

For Step 1, you must be able to:

- Explain the mechanism of action, common therapeutic uses, and adverse effects of acid-reducing therapies, laxatives, and antiemetics.
- Describe the use of lactulose and rifaximin in management of hepatic encephalopathy.
- List the medical therapies for management of gallstones and their limitations.
- Describe the use of pancreatic enzyme replacement in conditions of exocrine pancreas insufficiency.

1.1 Histamine-2 Receptor Antagonists

Histamine-2 receptor antagonists are widely used in the treatment of GERD. These drugs have a very good safety record and are available over the counter as well as by prescription. The most widely used histamine-2 receptor antagonists are ranitidine (Zantac), cimetidine (Tagamet), and famotidine (Pepcid).

Mechanism of Action The histamine-2 receptor is located on parietal cells and stimulates hydrochloric acid release upon activation by histamine. Histamine is released by enterochromaffin cells. The clinically used histamine-2 receptor antagonists are all competitive antagonists.

Therapeutic Uses Histamine-2 receptor antagonists are used extensively in the management of mild to moderate GERD. Because histamine-2 is only indirectly involved in gastric acid secretion, histamine-2 receptor antagonists are *not as effective as proton pump inhibitors in reducing gastric acid secretion*. Therefore, histamine-2-receptor antagonists would *not* be drug of choice for patients with severe reflux, such as may be seen in Zollinger-Ellison syndrome (very high acid production due to gastrinoma).

Adverse Effects Histamine-2 antagonists are fairly safe drugs. As discussed in Chapter 1, *cimetidine is an inhibitor of cytochrome P450 (CYP)* isoforms and can thus cause drug-drug inhibitors by interfering with the metabolism of drugs such as cyclosporine, tacrolimus, theophylline, and warfarin. Ranitidine and famotidine do not have this pharmacokinetic effect and are generally preferred over cimetidine for this reason. Histamine-2 antagonists can also affect the bioavailability of drugs such as fluoroquinolone and ketoconazole that are absorbed better in acidic conditions in the gastrointestinal tract.

Important Concept

As an inhibitor of CYP3A4, cimetidine is subject to problem drug-drug interactions with drugs such as cyclosporine, tacrolimus, theophylline, and warfarin.

1.2 Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are the most effective blockers of gastric acid secretion, making them highly useful for management of severe GERD. Multiple drugs with similar therapeutic effectiveness are on the market, including *omeprazole* (Prilosec), *lansoprozole* (Prevacid), and *pantoprazole* (Protonix).

Mechanism of Action PPIs are irreversible inhibitors of the K^+/H^+ antiporter ("proton pump") in the gastric parietal cell. By targeting the terminal step in acid release, PPIs reduce gastric acid secretion by up to 99%.

Important Concept

Proton pump inhibitors, as the most effective acid reducers, are the drugs of choice for severe GERD.

Therapeutic Uses PPIs are first-line therapy for patients with *peptic ulcers* and for *severe GERD*, including *Zollinger-Ellison syndrome*.

Adverse Effects The major concerns with PPIs are with long-term use. This occurs because the dramatic drop in acid secretion they bring about limits protein digestion and the absorption of vitamin B_{12} and calcium. Long-term use is associated with *bone fractures,* community-acquired pneumonia, atrophic gastritis, and *pseudomembranous colitis*. It is hypothesized that disruption of gastric pH can cause chronic changes in microbial flora in the gut. In general, patients should be on lowest dose possible of proton pump inhibitors and avoid long-term use, if feasible.

1.3 Antacids

Antacids are commonly used drugs that neutralize protons in the gut lumen. They are intended for *short-term relief of reflux-related symptoms*. Long-term use should be avoided, if possible.

One of the major risks of antacids is electrolyte disturbances, especially with chronic use. Renal failure patients are particularly at risk for this problem with aluminum- and magnesium-containing antacids.

1.3.1 Aluminum Hydroxide

Aluminum hydroxide is an uncommonly used antacid. These antacids should be avoided in renal failure patients due to risk of aluminum accumulation and toxicity.

1.3.2 Calcium Carbonate

Calcium carbonate is the active ingredient in a number of generic antacids (Tums, Rolaids).

1.3.3 Magnesium Hydroxide

Magnesium hydroxide is also a commonly used antacid. Magnesium-containing antacids should be avoided or used with caution in renal failure patients due to risk of magnesium overload.

1.3.4 Sodium Bicarbonate

Sodium bicarbonate is a simple antacid that can be made at home by mixing baking soda and water.

1.4 Sucralfate

Sucralfate polymerizes on the gastric luminal surface to form a *protective gel-like coating of ulcer beds*. Sucralfate is generally used in patients with known gastric ulcers and improves healing of ulcers and limits their recurrence. The main adverse effect is constipation or bezoar formation.

1.5 Prostaglandin Analogs

Prostaglandin analogs protect the gastric mucosa by increasing mucus and bicarbonate secretion. *Misoprostol* is the prototype drug in this class and is marketed both on its own and in combination with the NSAID diclofenac (Arthrotec).

Mechanism of Action Misoprostol is a *prostaglandin* E_1 *(PGE*$_1$*) analog* that *stimulates bicarbonate and mucus protection* in the gastric mucosa. (Note that this same prostaglandin also has action on the uterus, hence the use of misoprostol to treat missed miscarriage, stimulate stalled labor, and induce abortion.)

Therapeutic Uses Misoprostol is approved for use in the prevention of NSAID-induced gastric ulcers. It is particularly useful for those who have ulcers but need to take NSAIDs for other conditions (such as arthritis and prevention of myocardial infarction).

Adverse Effects The most common adverse effect of misoprostol is diarrhea. Misoprostol *should not be used in pregnant women due to risk of miscarriage or premature labor* by increase of uterine contractions.

1.6 Therapies to Eradicate *Helicobacter pylori*

Helicobacter pylori is a gram-negative bacterium implicated in *peptic ulcer disease*. Chronic infection with *H. pylori* increases risk of peptic ulcers and gastric stomach. *H. pylori* is difficult to eradicate and requires combination therapy.

1.6.1 Treatment Strategies

Therapies to eradicate *H. pylori* generally combine acid reduction (proton pump inhibitors or histamine-2 antagonists) with multiple antibiotics. *H. pylori* is often buried within gastric mucus.

1.6.2 Examples of Triple Therapies

There are a variety of combination therapies for *H. pylori*. Examples include:

- Omeprazole, amoxicillin, and metronidazole
- Omeprazole, clarithromycin, and amoxicillin
- Tetracycline, metronidazole, and bismuth

Antibiotic-resistant *H. pylori* can require more aggressive quadruple therapies.

Important Concept

Omeprazole plays a decisive role in many triple therapies.

1.7 Interventional Procedures

Gastric bleeding may require interventional procedures, especially for serious acute bleeding. These procedures use endoscopy combined with one of the techniques below to stop bleeding.

1.7.1 Thermal Contact Devices

Thermal contact devices use *cautery* (heat) or *electrical current* to stop bleeding. A common technique is *argon plasma coagulation,* whereby an electric current introduces a superficial burn to provide coagulation.

1.7.2 Sclerosing Agents

Another approach to stop bleeding is to inject a *sclerosing agent* such as ethanolamine or absolute ethanol. These agents *cause scarring* and constriction of the bleeding vessels.

2 Laxatives

Laxatives are foods or drugs that soften stools and stimulate bowel function. They are prescribed to relieve constipation.

2.1 Overview of Laxatives

Laxatives range from dietary fiber to drugs that influence gut motility. Some laxatives carry risks of adverse effects such as electrolyte disturbances.

2.2 Saline Laxatives

Saline laxatives exert *osmotic pressure* to retain water in the colon, thereby softening stools. The most common saline laxative is *magnesium sulfate*. The main risk of magnesium sulfate is in renal failure patients, who may develop hypermagnesemia. Saline laxatives can produce strong, fast laxative effects that may be undesirable in some patients.

2.3 Bulk Forming Laxatives (Dietary Fiber)

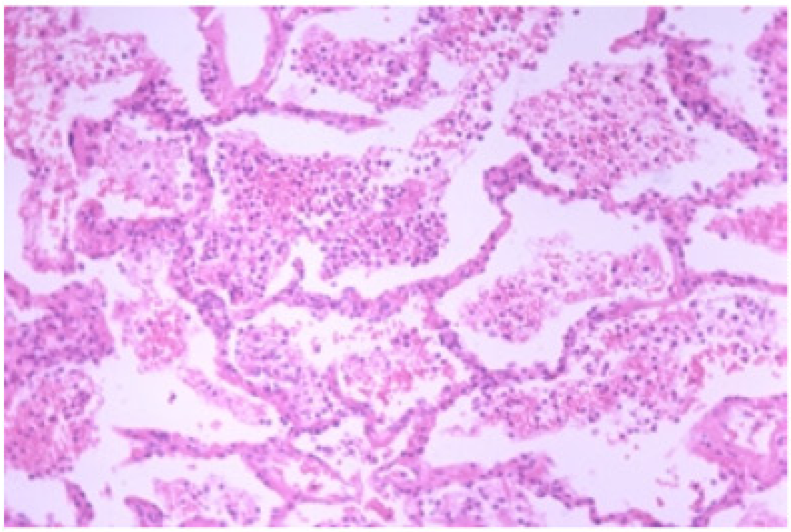
Bulk-forming laxatives include foods with high dietary fiber as well as medications (often available over-the-counter) with purified fiber. *Fiber is the safest of the laxatives,* with low risk of serious adverse effects; however, in patients with severe constipation due to lack of intestinal motility, bulk laxatives may predispose to obstruction.

2.4 Surfactant Laxatives (Docusate)

Surfactant laxatives include docusate. This class of laxative allows *water and fats* to be incorporated into stool. Surfactant laxatives can cause cramps and alter absorption of other drugs. Docusate is commonly used to treat *opioid therapy-related constipation,* although it may not be effective on its own.

2.5 Mineral Oil

Mineral oil acts as a lubricant and stool softener. Mineral oil can cause malabsorption of fat-soluble drugs and vitamins. A rare adverse effect is *lipoid pneumonia*, a form of lung inflammation that occurs when lipids enter the bronchial tree.

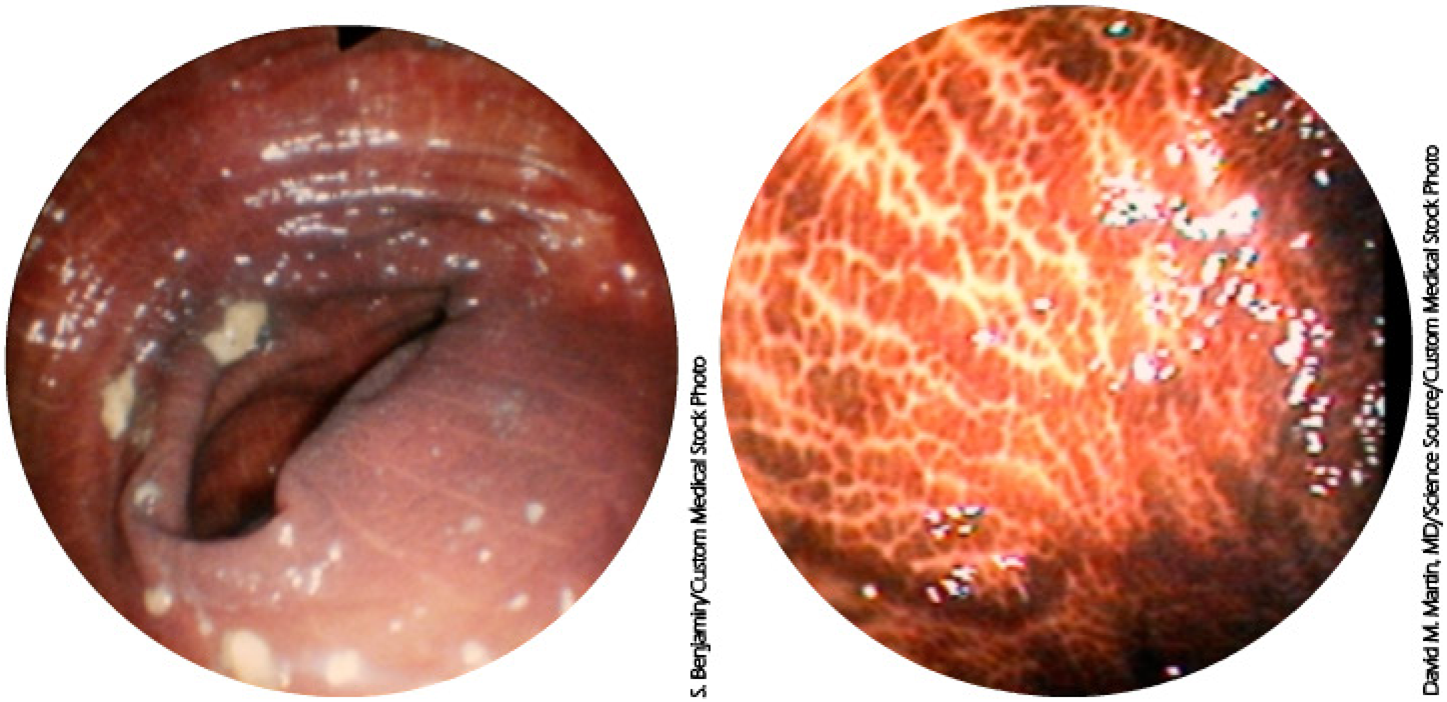


Carolina Biological Supply Co/Visuals Unlimited, Inc.

▲ **Figure 8–2.5** Lipoid Pneumonia

2.6 Stimulant Laxatives

Stimulant laxatives stimulate intestinal motility. Examples include *bisacodyl, castor oil,* and anthraquinones such as *cascara* or *senna*. Anthraquinone laxatives can discolor urine and cause melanotic (black-brown) staining of the colon (melanosis coli). Stimulant laxatives can be especially helpful in patients whose constipation is related to *slow intestinal peristalsis,* as in patients on opioid therapy.



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▲**Figure 8–2.6** Normal Colonic Mucose (left) and Melanosis Coli (right)

2.7 Laxative Abuse

Laxatives are sometimes abused, most often by patients with eating and/or body image disorders. Chronic overuse of laxatives can cause malabsorption of nutrients and drugs as well as electrolyte disturbances.

3

Drugs for Treatment of Nausea and Vomiting

Nausea and vomiting are common clinical problems. In some patients, such as those receiving cancer chemotherapy, nausea can be debilitating.

3.1 Therapeutic Targets

There are two primary physiologic targets for treatment of nausea and vomiting: *chemoreceptor trigger zone* and the labyrinthine/vestibular system.

3.1.1 Chemoreceptor Trigger Zone in the Area Postrema of the Brain

The chemoreceptor trigger zone is located in the *area postrema*, a structure in the base of fourth ventricle in medulla. The main receptors located here are for *serotonin-3 (*5-HT_3*) and dopamine*.

3.1.2 Labyrinthine and Vestibular Systems

The labyrinthine and vestibular systems are located in the *inner ears*. Disturbances of this system can lead to *vertigo* and *nausea*. The most effective pharmacotherapy of nausea related to these systems are *anticholinergic* and *antihistamine* drugs.

3.2 Anticholinergics and Antihistamines

Anticholinergic (antimuscarinic) and antihistamine drugs are commonly used for treatment of nausea and vomiting.

3.2.1 Diphenhydramine

Diphenhydramine is an antagonist of *histamine-1* and *muscarinic* receptors. Diphenhydramine is useful for benign positional vertigo and motion sickness. Common effects of diphenhydramine are drowsiness and dry mouth.

3.2.2 Meclizine

Like diphenhydramine, meclizine is an antagonist of both *histamine-1* and *muscarinic* receptors, and is commonly used for prevention of *motion sickness*. Meclizine has a good safety record in pregnancy (FDA category B).

3.2.3 Scopolamine

Scopolamine is a potent *antimuscarinic* used primarily for prevention of motion sickness. It may be given transdermally as a *patch*.

3.3 Dopamine-2 Receptor Antagonists

The dopamine-2 receptor blockers are first-line therapies for nausea, particularly in the hospital setting.

3.3.1 Prochlorperazine (Compazine)

Prochlorperazine is very commonly used for nausea. The main adverse effect is dystonia due to excessive blockage of dopamine receptors.

3.3.2 Metoclopramide (Reglan)

Metoclopramide is an antiemetic and gastric prokinetic agent. It is particularly useful for nausea secondary to gastroparesis. Metoclopramide should not be used in patients with bowel obstruction.

3.4 5-HT_3 Receptor Antagonists

5-HT_3 antagonists are very *effective antiemetics* that target receptors in the chemoreceptor trigger zone. They are used mainly for chemotherapy-induced nausea and vomiting. Agents available in the United States include ondansetron, granisetron, and palonosetron. Both oral and intravenous forms are available.

3.5 Dronabinol (Marinol)

Dronabinol is a synthetic form of *tetrahydrocannabinol* (found in cannabis) used to treat *nausea and vomiting associated with chemotherapy*. This agent can *stimulate appetite*. In addition to cancer treatment, it is used in diseases such as AIDS. Dronabinol is regulated as a Schedule III controlled substance, unlike marijuana, which is Schedule I.

The main adverse effects of dronabinol are *psychoactive side effects* similar to those caused by cannabis/marijuana use. Dronabinol also can trigger positive marijuana drug tests because these tests target tetrahydrocannabinol metabolites.

3.6 Aprepitant (Emend)

Aprepitant is a relatively new drug introduced in 2003 for *nausea and vomiting related to chemotherapy or surgery*. This *neurokinin 1 receptor antagonist* blocks effects of substance P, which is found in high concentrations in the chemoreceptor trigger zone. Aprepitant is very potent but also very expensive, limiting use to cases of severe nausea and vomiting.

4 Miscellaneous GI Drugs

Other drugs acting on the gastrointestinal system include therapies for hepatic encephalopathy, gallstones, and pancreatic enzyme replacement.

4.1 Treatments of Hepatic Encephalopathy

One of the effects of liver failure is *encephalopathy*. The pathophysiology of hepatic encephalopathy is complex, but is related in part to *elevated ammonia* levels that result from liver failure. *Lactulose* and *rifaximin* are two treatments that reduce the symptoms of hepatic encephalopathy.

4.1.1 Lactulose

Lactulose is used as a stool softener, but also reduces serum ammonia by trapping ammonia in the intestine. This agent can *substantially reduce serum ammonia* in patients with chronic hepatic encephalopathy.

4.1.2 Rifaximin

Rifaximin is an antibacterial agent related to rifamycin. It is licensed to treat traveler's diarrhea caused by *E. coli*. Rifaximin has orphan drug status for treatment of hepatic encephalopathy. The presumed mechanism of action for relieving symptoms of hepatic encephalopathy is via *reduction of intestinal bacteria* that generate ammonia as a waste product.

4.2 Medical Therapies for Gallstones

The most common therapy for gallstones is cholecystectomy. However, bile acids may be used as medical therapy for cholesterol gallstones. Bile acids are ineffective in calcified or pigmented gallstones.

Important Concept

If the gallstone is visible by x-ray, medical therapy with bile acids is unlikely to work.

4.2.1 Chenodeoxycholic Acid

Chenodeoxycholic acid is an older therapy for gallstones. Bile acids reduce cholesterol absorption and prevent formation of stones. The most common adverse effects are increased liver enzymes and diarrhea.

4.2.2 Ursodeoxycholic Acid

Ursodeoxycholic acid, or ursodiol, is the most common medical therapy for *cholesterol gallstones*. The most frequent adverse effects are diarrhea and constipation.

4.3 Pancreatic Enzyme Replacement

Exocrine pancreas dysfunction can result in malabsorption of lipids and carbohydrates due to lack of pancreatic lipase and amylase. Fat malabsorption can result in steatorrhea.

4.3.1 Pancreatin

Pancreatin is a mixture of *amylase, lipase,* and the *protease trypsin*. This mixture is used in conditions in which pancreatic secretions are deficient, which include *cystic fibrosis, pancreatitis,* and *surgical pancreatectomy*.

4.3.2 Pancrelipase

Pancrelipase is similar to pancreatin, but contains more lipase enzyme.

Review Questions Chapters 6–8

The following vignette applies to questions 1 and 2.

A 68-year-old male complains of dry cough of several months' duration together with increasing shortness of breath. A squamous cell carcinoma on his scalp was surgically removed five months ago and he received chemotherapy. Physical examination reveals a healed left temporal scalp lesion, scattered pulmonary rales and wheezing, and hypertrophic, darkened fingernails. Chest x-ray shows bilateral pulmonary infiltrates without evidence of metastatic disease.

1. What chemotherapy did he *most likely* receive for his squamous cell carcinoma?

A. Doxorubicin
B. Azathioprine
C. Paclitaxel
D. Bleomycin
E. Carboplatin

2. What is the *most likely* pathologic finding from a lung biopsy in this patient?

A. Pyemic lung abscess
B. Bronchiectasis
C. Interstitial pneumonitis with fibrosis
D. Diffuse alveolar damage with hyaline membranes
E. Pleural plaques

The following vignette applies to questions 3 and 4.

A 58-year-old female is receiving combination chemotherapy for breast carcinoma. After a week of therapy, she complains of suprapubic pain and gross hematuria. Cytoscopy shows hemorrhage and inflammation of the urinary bladder.

3. Which of the following drugs *most likely* caused these problems?

A. Cyclophosphamide
B. Cisplatin
C. Methotrexate
D Bleomycin
E. 5-Fluorouracil

4. What drug *most likely* would have prevented the complication in the previous question if given concurrently with the chemotherapy?

A. Penicillamine
B. MESNA (2-mercaptoethanesulfonate)
C. Folic acid
D. Allopurinol
E. Leucovorin

Chapters 6–8 Review Questions

5. A 13-year-old girl has asthma-related problems that bother her nearly every day and also wake her up every one to two nights. She is not able to exercise and has been to the emergency room "many times" for asthma. She also required one admission to the intensive care unit for endotracheal intubation. Which of the following medications is *most appropriate* for daily, long-term maintenance therapy?

A. Inhaled cromolyn sodium
B. Inhaled racemic epinephrine
C. Inhaled albuterol
D. Inhaled flunisolide
E. Theophylline (oral medication)

6. For this same patient, what pharmacologic agent given systemically is *most likely* indicated when she has a severe asthmatic attack with respiratory distress not relieved by inhaled drugs?

A. Zileuton
B. Albuterol
C. Prednisone
D. Terbutaline
E. Theophylline

7. A 55-year-old male presents to his primary care physician for progressive difficulties with breathing. He has had an 80-pack-a-year cigarette smoking history (2 to 3 cigarettes/day) and only recently quit smoking. He has difficulty walking more than a block at a time without stopping to catch his breath. He is referred for pulmonary function tests, which show a forced expiratory volume of 1 second (FEV_1) of 55%. What would be the *most appropriate* pharmacotherapy for this patient?

A. Inhaled tiotropium
B. Inhaled cromolyn sodium
C. Diphenhydramine
D. Theophylline
E. Zafirlukast

8. A 33-year-old female is having significant problems with allergy symptoms (runny and itchy nose), particularly in the summer and autumn. She is currently using diphenhydramine daily, which helped with her symptoms but is causing problems with drowsiness and difficulty urinating. What would be the *best* alternative pharmacotherapy for this patient?

A. Theophylline
B. Prednisone
C. Omalizumab
D. Tiotropium
E. Fexofenadine

Review Questions Chapters 6–8

The following vignette applies to questions 9 and 10.

An 18-year-old female presents to the emergency room with severe abdominal pain and a history of 10 days of profuse, watery diarrhea. She complains of dizziness when standing. Physical examination reveals hypotension (BP 75/40 mmHg), tachycardia (110 bpm), no fever, hyperactive bowel sounds, and dry mucous membranes.

Leukocyte count	5,000/mm^3 (normal 4,500–11,000)
Hemoglobin	11.5 g/dL (13.5–17.5)
Hematocrit	34.8% (41–53)
Platelet count	177,000/mm^3 (150,000–450,000)
Sodium	130 mEq/L (136–145)
Chloride	110 mEq/L (95–105)
Potassium	2.7 mEq/L (3.5–5.0)
Bicarbonate	19 mEq/L (22–28)

After receiving intravenous solutions of dextrose and electrolytes, the patient undergoes a sigmoidoscopy, which reveals intact colonic mucosa that is unusually dark brown in appearance.

9. Further questioning of the patient reveals that she has been trying to lose weight and has been taking a drug for this purpose. Extended use of which of the following drugs would *most likely* fit the clinical picture described above?

A. Castor oil
B. Docusate sodium
C. Senna
D. Dietary fiber
E. Mineral oil

10. What is the *most likely* cause of the darkened colonic mucosa seen on sigmoidoscopy?

A. Thrombosis
B. Bacterial overgrowth
C. Ischemia
D. Dehydration
E. Melanotic pigment deposition

Chapters 6–8 Review Questions

The vignette below applies to questions 11 and 12.

A 29-year-old female with end-stage AIDS is seen with chief complaints of anorexia and cachexia. She spends most of her time at home in bed because of weakness. Physical examination reveals a markedly underweight female with cachectic, sunken eyes, prominent skin wrinkles, and significant loss of skeletal muscle mass.

11. Which of the following pharmacological agents is *most likely* to help this woman increase her appetite?

A. Droperidol
B. Fluticasone
C. Dronabinol
D. Repaglinide
E. Chlorpropamide

12. What is the *most likely* adverse effect associated with this medication?

A. Pulmonary hypertension
B. Diarrhea
C. Bradycardia
D. Unusual thoughts
E. Cyanosis

Review Answers Chapters 6–8

1. The correct answer is D. The clinical vignette is strongly suggestive of pulmonary fibrosis (interstitial lung disease). Of the agents listed, bleomycin would be the one most commonly to cause that effect.

2. The correct answer is C. Interstitial pneumonitis with fibrosis would be the expected pathology from *bleomycin-induced pulmonary fibrosis*.

3. The correct answer is A. The patient's presentation is consistent with hemorrhagic cystitis, which is commonly caused by *cyclophosphamide*.

4. The correct answer is B. The hemorrhagic cystitis caused by cyclophosphamide is mediated by a toxic metabolite known as acrolein. *MESNA* detoxifies acrolein and limits risk of cystitis.

5. The correct answer is D. Inhaled flunisolide. This patient has severe, persistent asthma according to the guidelines of the National Asthma Expert Panel of the NIH (continuous symptoms, frequent nocturnal symptoms, many ER visits, etc.). She needs chronic therapy with an inhaled corticosteroid such as flunisolide (Aerobid). If this is not effective, she may require oral (systemic) prednisone, although hopefully this can be minimized to avoid the well-known toxic effects associated with long-term systemic corticosteroid therapy (osteoporosis, diminished wound healing, etc.). Cromolyn sodium, racemic epinephrine, and albuterol are appropriate therapy in some circumstances for *acute exacerbations* but are not suitable for daily, long-term use. Theophylline can be used chronically but is no longer a first-line agent for asthma.

6. The correct answer is C. Prednisone, a corticosteroid, is a very effective treatment for severe asthma exacerbation. In this patient, who has already required previous hospital admissions for asthma, aggressive therapy is indicated. Prednisone is given orally. Alternatively, prednisolone is similar to prednisone but is administered intravenously. Zileuton is for chronic management of asthma. Albuterol is used for acute exacerbations but the case states that the patient is beyond being responsive to inhaled drugs.

7. The correct answer is A. Inhaled tiotropium, a long-acting muscarinic receptor antagonist bronchodilator, is one of the recommended therapies for moderate (stage II) COPD, which this patient has. An alternative would be salmeterol (long-acting β2-adrenergic agonist). This patient also should start chronic therapy with inhaled corticosteroid.

8. The correct answer is E. Fexofenadine is a second-generation antihistamine with far less-sedating effects than diphenhydramine. This would be the best alternative to try for this patient. The other options would be inappropriate choices for allergic rhinitis.

9. The correct answer is C. Senna. The clinical picture is consistent with chronic laxative abuse, which has resulted in diarrhea, dehydration, and electrolyte disturbances. The darkened color in the colonic mucosa is most likely *melanosis coli*, which is due to melanotic pigment deposition by an anthraquinone laxative such as Senna. While misuse of castor oil and docusate might cause diarrhea and dehydration, these agents would not stain the colon. Bulk fiber would be unlikely to cause adverse effects.

Chapters 6–8 Review Answers

10. The correct answer is E. Melanotic pigment deposition. The darkened colonic mucosa in melanosis coli due to anthraquinolone is benign and does not require any treatment. The main risk would be confusion of the darkened colonic mucosa with another entity such as Peutz-Jehgers syndrome.

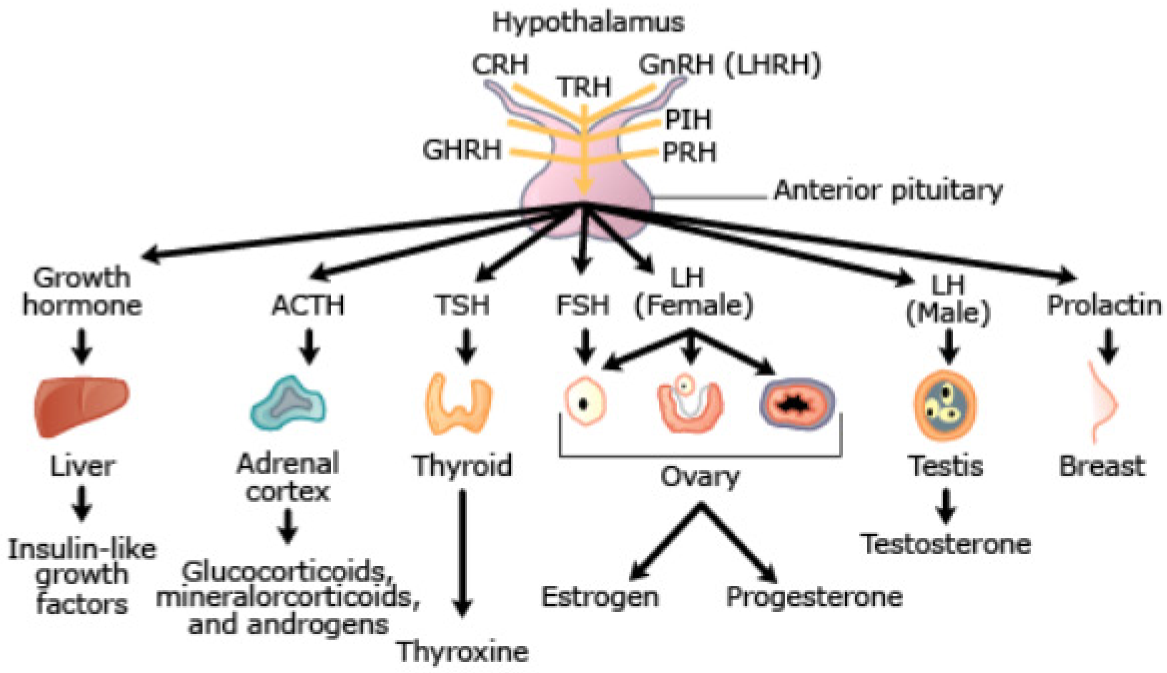
11. The correct answer is C. Dronabinol is a synthetic tetrahydrocannabinol that increases appetite. Droperidol is an anti-nausea agent that is not as effective as dronabinol in stimulating appetite. Fluticasone is a steroid used in asthma therapy. Repaglinide and chlorpropamide are used to treat type II diabetes.

12. The correct answer is D. One of the common adverse effects of dronabinol is psychoactive effects such as unusual thoughts or confusion. These adverse effects are the most common reason patients discontinue therapy with dronabinol. Dronabinol also can cause positive drug screens for cannabis/marijuana that can create issues for patients who need to undergo drug screening for work or some other situation.

CHAPTER 9 Endocrinology Drugs

1 Overview of the Endrocrine System

The endocrine system is regulated at multiple levels and affects every organ system. The ultimate control is via the hypothalamus and the pituitary gland. Hypothalamic peptide hormones are known as releasing hormones (e.g., corticotropin-releasing hormone, or CRH) and act on the pituitary gland. The pituitary in turn secretes hormones that act on target organs and tissues.


Hypothalamus
CRH
TRH
GnRH (LHRH)
PIH
PRH
GHRH
Anterior pituitary
Growth hormone
ACTH
TSH
FSH
LH (Female)
LH (Male)
Prolactin
Liver
Adrenal cortex
Thyroid
Ovary
Testis
Breast
Insulin-like growth factors
Glucocorticoids, mineralorcorticoids, and androgens
Thyroxine
Estrogen
Progesterone
Testosterone

▲ **Figure 9-1.0** Endocrine System

USMLE® Key Concepts

For Step 1, you must be able to:

- Describe the therapeutic uses and adverse effects of androgen, estrogen, glucocorticoid, mineralocorticoid, and progestogen drugs.
- Explain the therapeutic approaches used to manage type 1 and 2 diabetes and the adverse effects of insulin and oral hypoglycemic agent therapies.
- Identify the treatment strategies for managing hypothyroidism and hyperthyroidism and the adverse effects of these therapies.

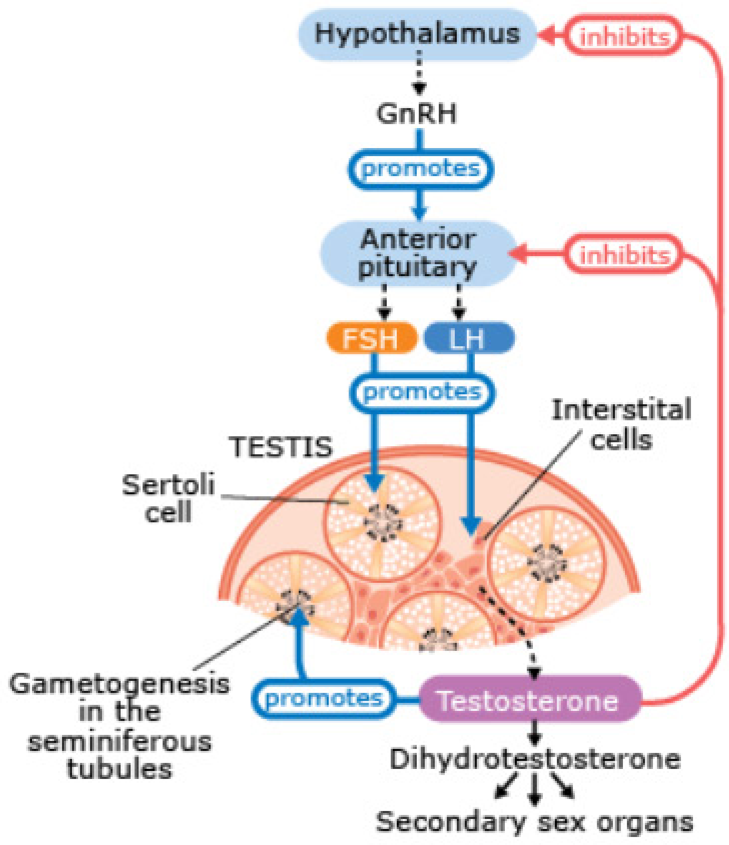
2

Androgens

Androgens are steroid hormones that activate the androgen receptor. The major androgen in humans is testosterone. Dihydrotestosterone is a metabolite of testosterone that is the most potent androgen for hair follicles and the prostate gland.

2.1 Testosterone

Testosterone is secreted by Leydig cells of the testes in response to luteinizing hormone (LH) from the anterior pituitary gland. Testosterone is not used clinically due to short half-life.


Hypothalamus
inhibits
GnRH
promotes
Anterior pituitary
inhibits
FSH
LH
promotes
Interstitial cells
TESTIS
Sertoli cell
Gametogenesis in the seminiferous tubules
promotes
Testosterone
Dihydrotestosterone
Secondary sex organs

▲ **Figure 9-2.1A** Regulation of Androgen Hormones

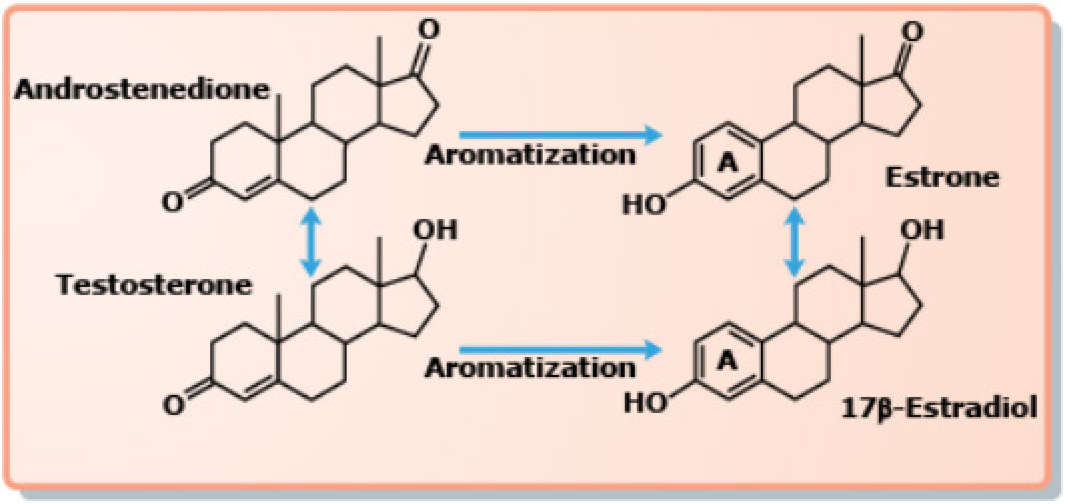
2.1.1 Cellular Actions

There are three main metabolic actions of testosterone:

- Testosterone binds to androgen receptors in target tissues.
- Testosterone can be converted to *5α-reductase* and then to dihydrotestosterone, which also acts at androgen receptors. Hair follicles and the prostate gland are the two main tissues that are responsive to dihydrotestosterone.
- Testosterone can be converted to estradiol, which binds to the estrogen receptor.

2.1.2 Conversion to Estrogens

The conversion of androgens to estrogens (e.g., testosterone to estradiol) is termed *aromatization* (because of the introduction of an aromatic ring into the steroid structure).



▲ **Figure 9-2.1B** Aromatization

2.1.3 Therapeutic Uses

The main indication for testosterone derivatives is treatment of male hypogonadism. The common causes for male hypogonadism are:

- Acquired damage or removal of testes (trauma, surgery, infection).
- Decline in testosterone production with aging. Repletion of testosterone has been shown to have multiple benefits in the older males.
- Genetic, most common of which is Klinefelter syndrome (47,XXY).

2.1.4 Clinically Used Derivatives of Testosterone

Testosterone esters (e.g., testosterone undecanoate) are commonly used clinically. The two main types of testosterone are transdermal patches and long-acting intramuscular "depot" injections.

2.1.5 Anabolic Steroids

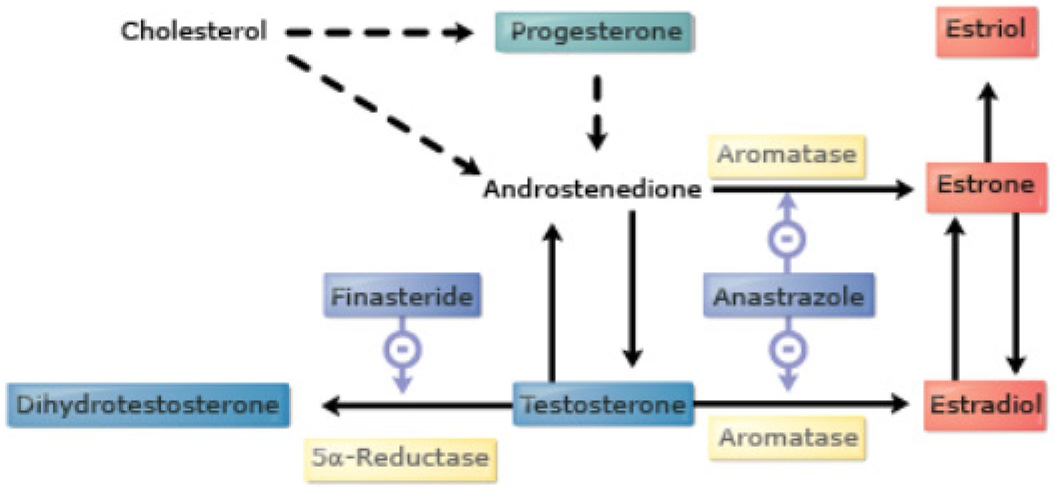
Anabolic steroids are androgen derivatives which, among other effects, increase muscle mass. These drugs have legitimate clinical uses but also are used illicitly to boost athletic performance (an example of "performance-enhancing drugs"). There are many examples but three common anabolic steroids are methyltestosterone, oxandrolone, and stanazolol.

Anabolic steroids have a variety of adverse effects, including:

- Aggressive behavior
- Acne
- Gynecomastia (due to conversion to estrogens)
- Testicular atrophy with impotence (androgen therapy causes inhibition of luteinizing hormone and reduction of endogenous production)
- Hypertension
- Hepatic neoplasia (at risk for bleeding)
- Glucose intolerance
- Decreased HDL levels
- Alopecia
- Amenorrhea (women)

2.2 Treatment of Prostate Disorders

The prostate gland is strongly affected by dihydrotestosterone, which stimulates growth, including the possible progression of prostate cancer and benign prostatic hypertrophy. Antiandrogen therapy is a therapeutic option for metastatic prostate cancer. Such therapy may either block the androgen receptor or inhibit 5α-reductase and thereby reduce dihydrotestosterone production.



▲**Figure 9-2.2** Antiandrogen Therapy

2.2.1 Flutamide/Leuprolide

Flutamide is used with leuprolide for prostate carcinoma. Flutamide is a competitive antagonist of the androgen receptor which blocks the binding of dihydrotestosterone to prostate androgen receptors.

One consequence of flutamide is feedback stimulation of gonadotropin-releasing hormone (GnRH) and luteinizing hormone. This is because blockade of androgen receptors is interpreted by the hypothalamus as a deficiency of testosterone. Leuprolide is a GnRH agonist that is administered in a sustained fashion to block this feedback stimulation cycle.

2.2.2 Cyproterone

Cyproterone is a partial agonist at androgen receptors. Cyproterone can be used for prostate cancer. Other clinical uses are:

- Curbing male precocious puberty.
- Treatment of male sexual offenders ("chemical castration").
- Reducing the effect of excess androgens in polycystic ovary syndrome (PCOS).

2.2.3 Spironolactone

Spironolactone is a potassium-sparing diuretic but it also has antagonist effects on androgen receptors. Spironolactone is sometimes used to manage the hyperandrogenism in PCOS.

2.2.4 5α-Reductase Inhibitors

Finasteride and dutasteride are drugs that inhibit 5α-reductase inhibitors and thereby block production of dihydrotestosterone. These are used for the treatment of benign prostatic hypertrophy and to stimulate hair growth in male pattern baldness (hair follicles are inhibited by dihydrotestosterone).

3 Estrogens

Estrogens are a group of steroid hormones with actions at many tissues in the body. The most potent natural estrogen is 17β-estradiol (commonly just called estradiol). Estrogens are largely bound to plasma protein in the bloodstream.

3.1 Overview of Estrogen Receptors

Activation of estrogen receptors by estrogen produces many effects including:

- Normal sexual maturation
- Uterine growth (myometrium and endometrium)
- Breast growth
- Decreased bone resorption (bone protection)
- Increased HDL, decreased LDL (both positive effects on lipids)
- Blood clotting

3.2 Clinical Uses

Estrogens are used for a variety of purposes:

- Oral contraceptives (either alone or in combination with progestogens)
- Hormone replacement therapy in postmenopausal women
- Female hypogonadism
  - Acquired (e.g., surgical removal of ovaries)
  - Congenital (most common being Turner syndrome: 45,XO)
- Dysmenorrhea
- Abnormal uterine bleeding

3.3 Adverse Effects

Estrogens, especially at higher doses, can produce a variety of adverse effects, including:

- Nausea
- Bloating
- Headache
- Mastalgia
- Thromboembolism
  - Synthetic estrogens such as ethinyl estradiol are much more thrombogenic than endogenous estradiol.
  - Risk of abnormal clotting increased if other risk factors for thrombosis are present (e.g., Factor V Leiden, cigarette smoking, etc.).
- Increased risk of breast cancer
- Increased risk of endometrial cancer

Contraindications to Estrogen Therapy Because of the potential adverse effects of synthetic estrogens, especially when used for contraception, there are a number of clinical situations in which estrogen therapy is relatively or absolutely contraindicated. These contraindications include the presence or history of:

- Thromboembolic disease
- Genetic mutation increasing risk of abnormal clotting
    - Factor V Leiden
    - Protein C deficiency
    - Protein S deficiency
    - Prothrombin variant
- Cerebral vascular disease
- Myocardial infarction
- Coronary artery disease
- Congenital hyperlipidemia
- Cigarette smoking (particularly if over age 35)
- Carcinoma of the breast
- Carcinoma of the female reproductive tract
- Abnormal vaginal bleeding of unknown cause
- Known or suspected pregnancy
- Liver tumors or impaired liver function

3.4 Clinically Prescribed Estrogens

Clinically used synthetic estrogens are designed for increased oral bioavailability and therapeutic half-life. Unmodified estradiol has a very short half-life and is not used clinically.

3.4.1 Conjugated Equine Estrogens

Conjugated equine estrogens (e.g., Premarin) are estrogen sulfate esters used primarily for hormone replacement therapy in postmenopausal women.

3.4.2 Ethinyl Estradiol

Ethinyl estradiol is a synthetic estrogen found in a number of oral contraceptives.

3.5 Diethylstilbestrol

Diethylstilbestrol (DES) is a synthetic estrogen used decades ago for the prevention of threatened abortion. DES was eventually taken off the U.S. market because of teratogenic effects.

Exposure of female fetuses to DES in the first trimester was associated with urogenital tract abnormalities including the persistence of müllerian glands on the upper vagina and clear-cell adenocarcinoma of the vagina (an otherwise very rare malignancy). Exposure of male fetuses was associated with cryptorchidism and hypospadias.

3.6 Selective Estrogen Receptor Modulators (SERMs)

Selective estrogen receptor modulators (SERMs) are drugs with tissue-specific estrogenic activity. A SERM may have estrogen agonist activity in some tissues and no activity or antagonistic activity in other tissues. The goal is to produce beneficial estrogen effects in some target tissues (e.g., prevent bone loss) but to avoid deleterious effects, such as an increased risk of breast and endometrial cancer.

3.6.1 Tamoxifen

Tamoxifen is a SERM with the following profile:

- Antagonist activity at breast estrogen receptors (ERs)
- Partial agonist activity at endometrial ERs
- Agonist activity at bone ERs

The major therapeutic use of tamoxifen is the treatment of estrogen-receptor positive breast cancer. The adverse effects of tamoxifen include menopausal-like symptoms (e.g., hot flashes, vaginal discharge/bleeding, menstrual irregularities, painful intercourse), thromboembolism, fatty liver disease, and an increased risk of endometrial cancer.

Important Concept

One of the key tests for newly diagnosed breast cancer is estrogen receptor status. Estrogen receptor-positive breast cancers can be treated with estrogen-related therapies such as tamoxifen and anastrozole.

3.6.2 Raloxifene

Raloxifene is a SERM that is very selective as an estrogen agonist for bone ERs. Raloxifene is used to treat osteoporosis and does not increase the risk of estrogen-dependent breast and endometrial cancers.

3.6.3 Clomiphene

Clomiphene is an ER antagonist at all tissues studied. Clomiphene is used as a fertility drug and acts by blocking anterior pituitary ERs, which play a role in sensing circulating estradiol levels. When dosing is timed appropriately, clomiphene influences FSH secretion in a manner that increases ovulation. One caution of clomiphene as a fertility drug is an increased incidence of multiple conceptions (i.e., twins, triplets, quadruplets, etc.).

3.7 Aromatase Inhibitors

Aromatase inhibitors block the conversion of androgens to estrogens. Examples include anastrozole, exemestane, and letrozole. These drugs are approved for the treatment of estrogen-receptor positive breast cancers in postmenopausal women. Aromatase inhibitors also are used by men abusing anabolic steroids to avoid gynecomastia due to aromatization of androgens.

4 Progestogens

Progestogens are steroid hormones produced by the adrenal glands, ovaries, placenta, and testes. The natural progestogens include pregnenolone, 17α-hydroxypregnenolone, progesterone, and 17α-hydroxyprogesterone. Synthetic derivatives of progesterone are the progestogens most commonly used clinically.

Clinical Application

The adverse effects of progestogen drugs resemble common symptoms of polycystic ovary syndrome.

4.1 Overview of Progestogens

Progestogens are precursors to the androgens, estrogens, and glucocorticoids. Progesterone is the major progestogen active at the progesterone receptor. The biological effects of progesterone include:

- Maturation of endometrium
- LH surge
- Breast growth (alveolobular)

Important Concept

Mifepristone is not to be confused with the "morning-after pill", which consists of two doses of estrogen and progestogen at approximately two times the normal dose of combination contraception pills.

4.2 Clinical Uses

The major clinical uses of progestogens are as follows:

- Combination with estrogen hormone replacement to decrease the risk of estrogen-sensitive cancers (breast, endometrium).
- Progestogen-only oral contraceptive:
  - Recommended for lactating women.
  - However, increased incidence of breakthrough menstrual bleeding in progestogen-only contraceptives.
- Combination oral contraceptives (progestogen and estrogen together): Reduces breakthrough menstrual bleeding.

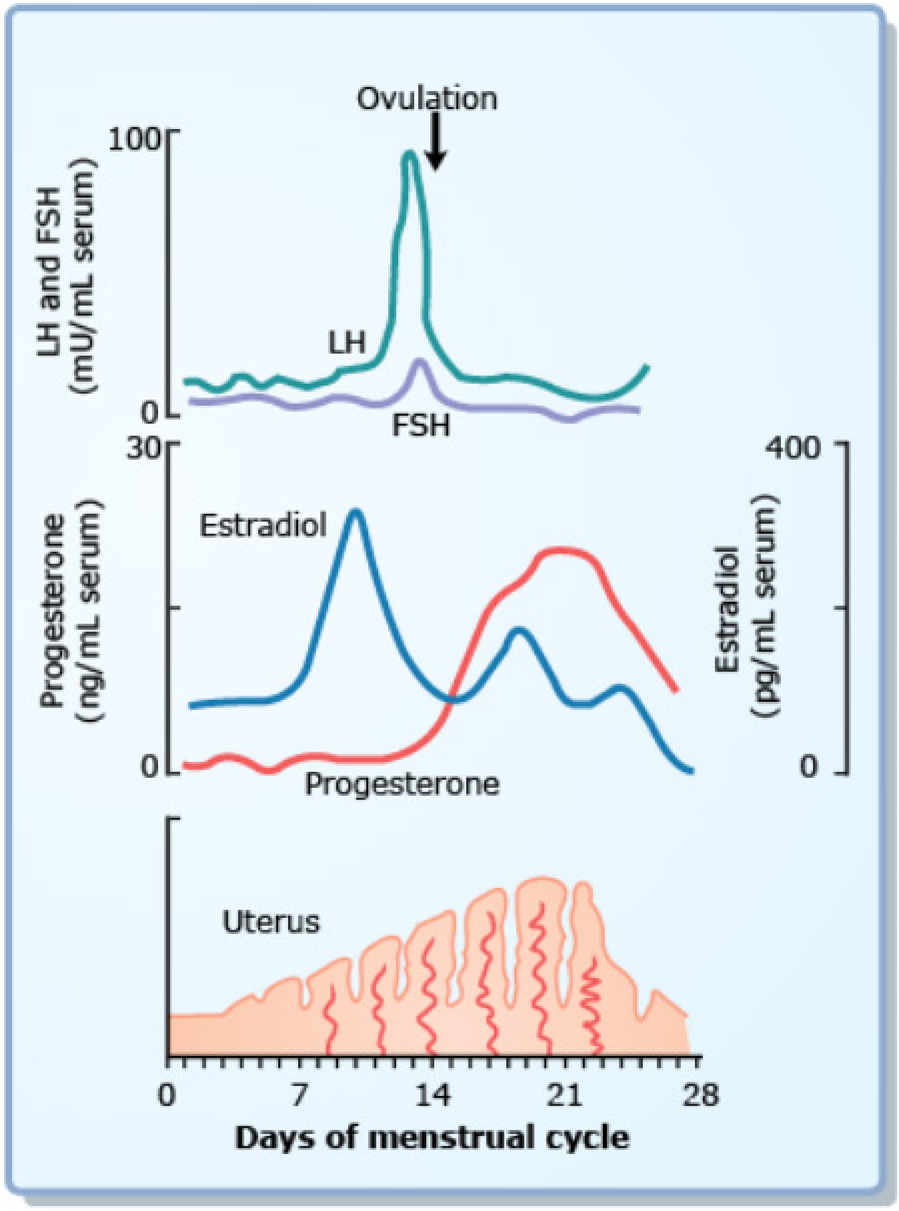
4.3 Adverse Effects

The adverse effects of progestogens include:

- Weight gain
- Hirsutism
- Acne
- Tiredness
- Depression

4.4 Mifepristone (RU-486)

Mifepristone is an antiprogestogen that is used to induce abortion (sometimes referred to as the "abortion pill"). Mifepristone is followed by a dose of misoprostol at 48 hours to induce uterine contraction and expulsion.



▲**Figure 9-4.1** Combination Oral Contraceptives

5 Adrenocortical Steroids

The adrenal cortex can synthesize the full range of steroid hormones, including androgens, estrogens, glucocorticoids, mineralocorticoids, and progestogens. The glucocorticoids and mineralocorticoids often are referred to as the corticosteroids.

5.1 Overview of Corticosteroids

The corticosteroids have numerous and widespread effects throughout the body, including on metabolism (carbohydrate, protein, and lipids), blood pressure, salt retention, the immune system, and the nervous system.

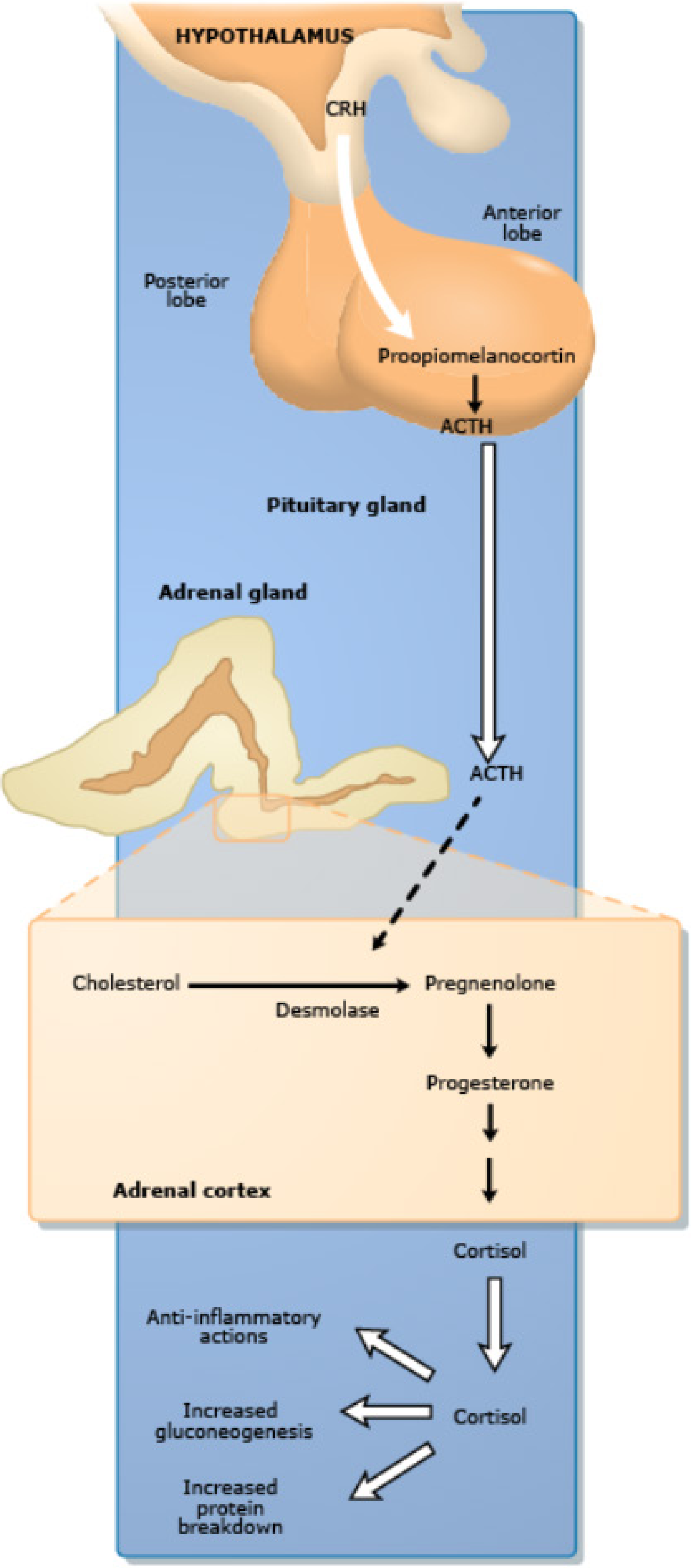
5.2 Glucocorticoids

The glucocorticoids are a group of steroid hormones that act at the glucocorticoid receptor. The major endogenous glucocorticoid is cortisol. Clinically used glucocorticoids are synthetic derivatives of cortisol. Glucocorticoid secretion is regulated by corticotrophin-releasing hormone (CRH) from the hypothalamus and adrenocorticotropin-releasing hormone (ACTH) from the anterior pituitary.

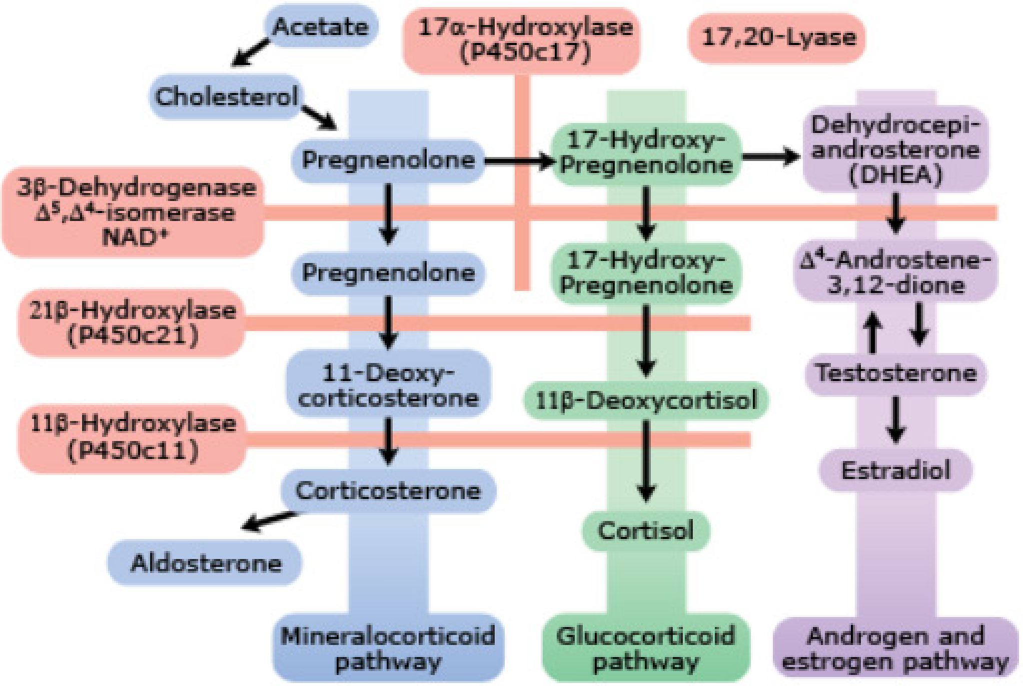
5.2.1 Therapeutic Uses

The glucocorticoids are used extensively in the management of inflammatory disorders and for their immunosuppressive actions. Other therapeutic uses include replacement therapy in syndromes of glucocorticoid deficiency and stimulation of fetal lung development.

Congenital Defects in Steroid Synthesis Congenital adrenal hyperplasia refers to a variety of autosomal recessive disorders that involve mutations in enzymes in the steroid synthesis pathway. The clinical symptoms depend on gender, which enzyme is affected, and the severity of the mutation. The treatment may include chronic glucocorticoid and mineralocorticoid therapy, which can be adjusted as needed.


HYPOTHALAMUS
CRH
Anterior lobe
Posterior lobe
Proopiomelanocortin
ACTH
Pituitary gland
Adrenal gland
ACTH
Cholesterol
Desmolase
Pregnenolone
Progesterone
Adrenal cortex
Cortisol
Anti-inflammatory actions
Increased gluconeogenesis
Increased protein breakdown
Cortisol

▲ **Figure 9-5.2A** Secretion and Action of ACTH


Acetate
17α-Hydroxylase (P450c17)
17,20-Lyase
Cholesterol
Pregnenolone
17-Hydroxy-Pregnenolone
Dehydrocepi-androsterone (DHEA)
3β-Dehydrogenase Δ^5,Δ^4-isomerase NAD⁺
Pregnenolone
17-Hydroxy-Pregnenolone
Δ^4-Androstene-3,12-dione
21β-Hydroxylase (P450c21)
11-Deoxy-corticosterone
11β-Deoxycortisol
Testosterone
11β-Hydroxylase (P450c11)
Corticosterone
Estradiol
Cortisol
Aldosterone
Mineralocorticoid pathway
Glucocorticoid pathway
Androgen and estrogen pathway

▲**Figure 9-5.2B** Steroid Synthesis

Treatment of Glucocorticoid Deficiency Glucocorticoid deficiency can occur in a variety of conditions, including:

- Autoimmune adrenal disease
- Damage to the hypothalamus or the pituitary gland (affecting CRH and/or ACTH)
- Shock, infection, or trauma affecting the adrenal gland

Infection Some patients in septic shock will require glucocorticoids to prevent adrenal insufficiency.

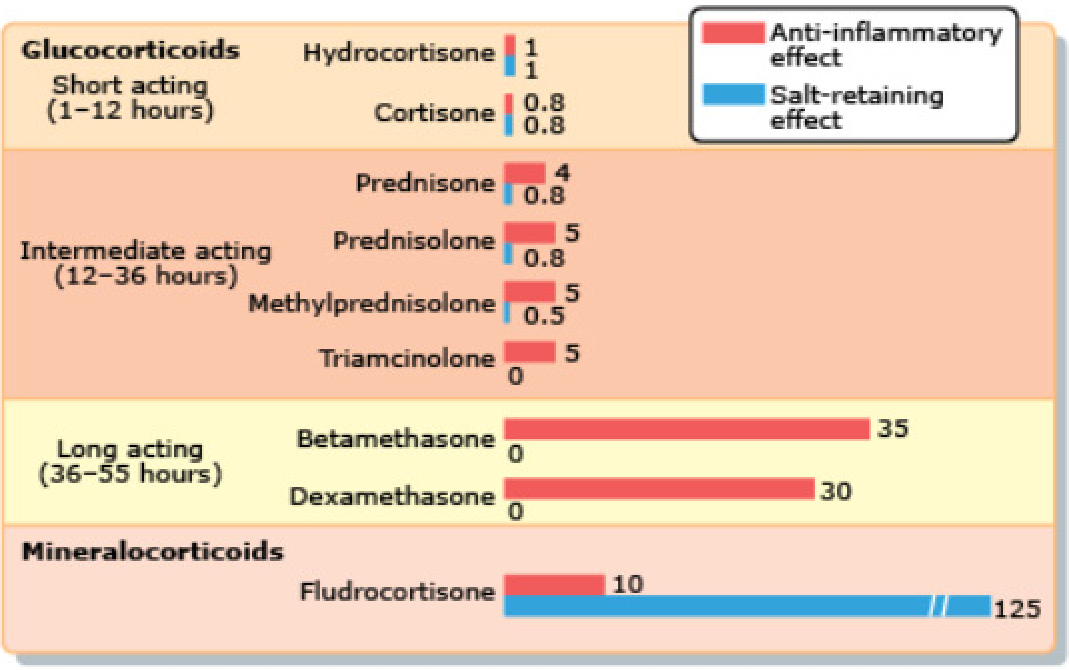
Fetal Lung Maturity Glucocorticoids stimulate fetal lung development and the production of surfactant. Betamethasone, dexamethasone, or hydrocortisone are typically given to pregnant women who are predicted to deliver prematurely (e.g., before 32 weeks' gestation).

Looking Back

The corticosteroids play a major role in asthma therapy. Inhaled corticosteroids commonly used to treat asthma include budesonide, beclomethasone, fluticasone, and mometasone. Systemic corticosteroids used include prednisone (oral) and prednisolone (intravenous).

5.2.2 Clinically Used Glucocorticoids

Compared with cortisol, the clinically used glucocorticoids are designed for good oral bioavailability, longer half-life, and less mineralocorticoid activity. The most common systemic glucocorticoids are hydrocortisone, prednisolone, prednisone, and betamethasone.

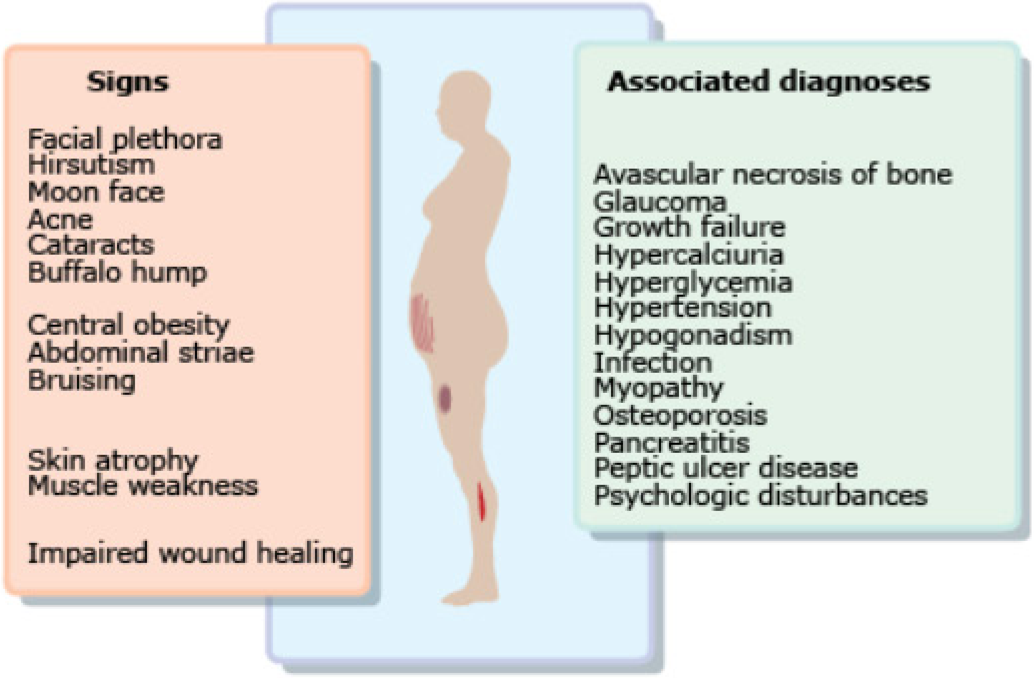


▶**Figure 9-5.2C** Glucocorticoids and Mineralocorticoids

5.2.3 Adverse Effects

Glucocorticoids have many potential adverse effects, particularly when they are used chronically. Cushing syndrome refers to any clinical scenario with excess glucocorticoids. Possible symptoms include:

- Altered fat deposition
- Muscle weakness/atrophy
- Striae
- Bruising
- Acne
- Hyperglycemia due to gluconeogenesis
- Osteoporosis
- Electrolyte imbalance
- Suppression of skeletal growth in children
- Decreased wound healing
- Suppression of the immune system
- Varied central nervous system effects (depression, psychosis, etc.)


Signs
Facial plethora
Hirsutism
Moon face
Acne
Cataracts
Buffalo hump
Central obesity
Abdominal striae
Bruising
Skin atrophy
Muscle weakness
Impaired wound healing
Associated diagnoses
Avascular necrosis of bone
Glaucoma
Growth failure
Hypercalciuria
Hyperglycemia
Hypertension
Hypogonadism
Infection
Myopathy
Osteoporosis
Pancreatitis
Peptic ulcer disease
Psychologic disturbances

▲ **Figure 9-5.2D** Cushingoid Side Effects of Glucocorticoids

Sustained therapy with glucocorticoids causes suppression of ACTH secretion and adrenal cortical atrophy. Chronic glucocorticoids should be tapered gradually to allow patients to restore adrenal function.

5.3 Mineralocorticoids

Mineralocorticoids are important in fluid and electrolyte balance. The main endogenous mineralocorticoid is aldosterone. Cortisol also has mineralocorticoid effects.

5.3.1 Fludrocortisone

For clinical treatment, fludrocortisone often is used as the specific mineralocorticoid in patients with adrenal insufficiency. The specificity of fludrocortisone and synthetic glucocorticoids allows physicians to more carefully titrate mineralocorticoid and glucocorticoid effects, rather than use a single drug with broader effects. Fludrocortisone is indicated in patients with adrenal insufficiency showing signs of low aldosterone (e.g., low plasma sodium levels).

Important Concept

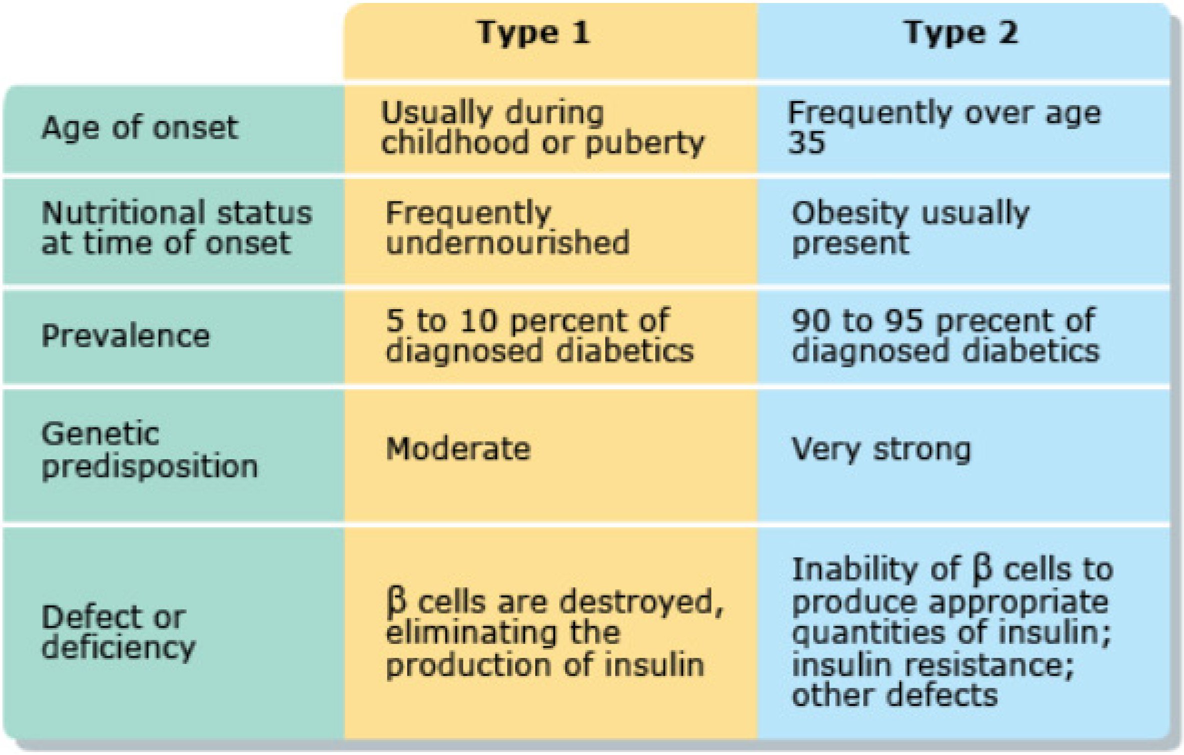
Chronic glucocorticoid therapy, particularly with high doses, should never be abruptly withdrawn because of the risk of acute adrenal insufficiency and shock state (Addisonian crisis).

6 Diabetes Therapy

Diabetes is a disease that is increasing in incidence, related in large part to increasing obesity. Diabetes therapy varies based on the type of diabetes.

6.1 Overview of Diabetes

Diabetes is integrally related to insulin, an anabolic hormone involved in metabolism of carbohydrates, amino acids, and fatty acids. There are two major types of diabetes.



	Type 1	Type 2
Age of onset	Usually during childhood or puberty	Frequently over age 35
Nutritional status at time of onset	Frequently undernourished	Obesity usually present
Prevalence	5 to 10 percent of diagnosed diabetics	90 to 95 precent of diagnosed diabetics
Genetic predisposition	Moderate	Very strong
Defect or deficiency	β cells are destroyed, eliminating the production of insulin	Inability of β cells to produce appropriate quantities of insulin; insulin resistance; other defects

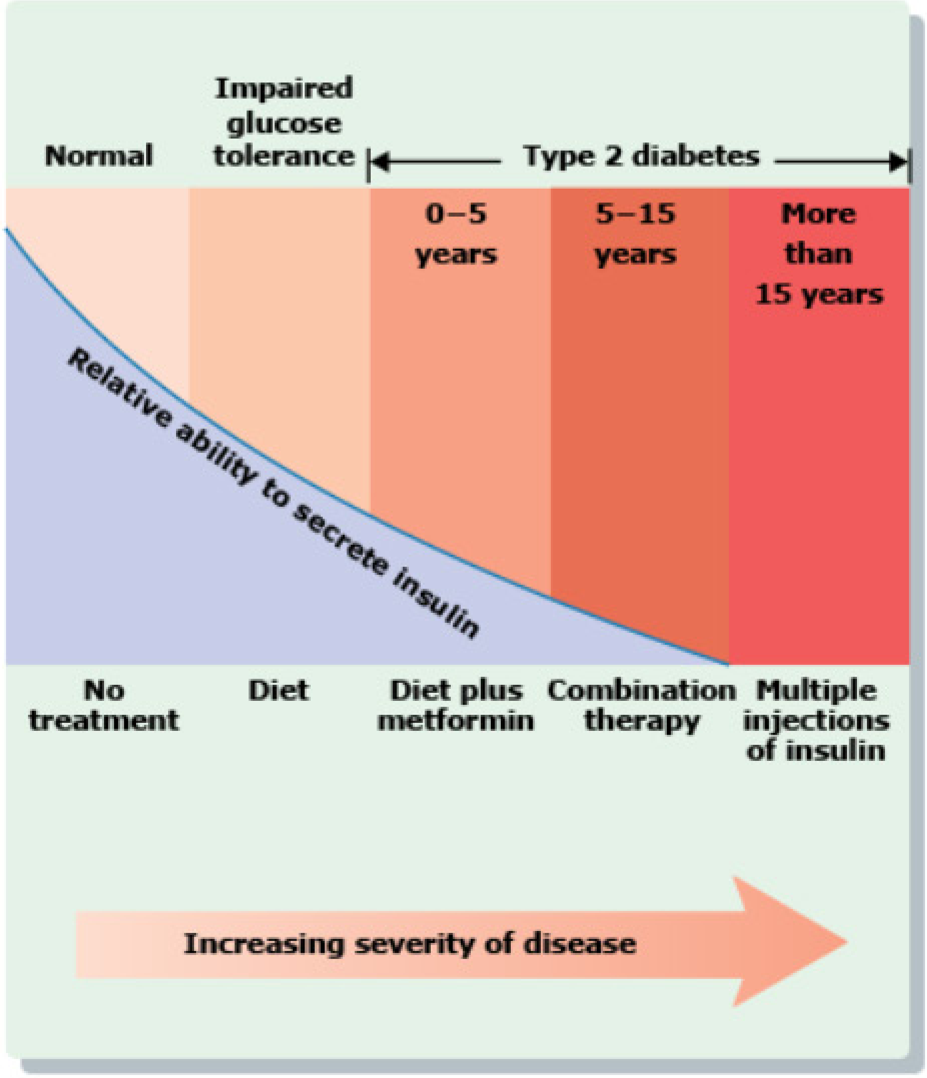
▲**Figure 9-6.1A** Type 1 and Type 2 Diabetes

6.1.1 Type 1 Diabetes

Type 1 diabetes (sometimes called "juvenile-onset") is an autoimmune disease in which there is loss of pancreatic β cells that synthesize insulin. Disease symptoms occur because of a deficiency of insulin. The standard therapy for type 1 diabetes is insulin replacement.

6.1.2 Type 2 Diabetes

Type 2 diabetes (formerly called "adult onset") is characterized by a lack of sensitivity to insulin. There is a strong association with obesity. Unlike type 1 diabetes, synthesis of insulin is not the problem; instead, there may be excess levels of insulin present.


Normal
Impaired glucose tolerance
Type 2 diabetes
0–5 years
5–15 years
More than 15 years
Relative ability to secrete insulin
No treatment
Diet
Diet plus metformin
Combination therapy
Multiple injections of insulin
Increasing severity of disease

▲**Figure 9-6.1B** Clinical Course of Type 2 Diabetes

6.1.3 Nonconventional Type 2 Diabetes

There are relatively uncommon forms of diabetes that present similarly to standard type 2 diabetes, yet are unusual because they occur at a young age. Collectively, these account for less than 1% of diabetes. Genetic defects that cause nonconventional type 2 diabetes include mutations in:

- Glucokinase
- Insulin molecule
- Insulin receptor
- Glucose transporters

6.1.4 Metabolic Syndrome

The metabolic syndrome is characterized by obesity (especially central obesity), elevated triglycerides (≥150 mg/dL), reduced HDL cholesterol (men <40 mg/dL, women <50 mg/dL), elevated blood pressure, and hyperglycemia. Patients with metabolic syndrome are at high risk for cardiovascular disease.

6.1.5 Diabetes Management

The cornerstone of initial diabetes management is diet modification and exercise routines. In some cases, weight loss can alleviate the symptoms of type 2 diabetes. Type 1 diabetics eventually require insulin replacement. Type 2 diabetics are managed with oral hypoglycemics with or without insulin.

6.1.6 Monitoring Diabetic Therapy

Plasma glucose measurements provide a single time point of glucose control. Glycosylated hemoglobin (HbA_{1c}) provides a measure of glucose control over a several-month period (life of erythrocyte). Current data recommends relatively tight control aiming for HbA_{1c} of 7% or less (equating to an average blood glucose of 150 mg/dL or less).

6.2 Insulin

Insulin therapy is the main therapy in type 1 diabetes. Patients with type 2 diabetes may require insulin therapy, especially in the late stages of the disease. There are a variety of insulin preparations available, ranging in onset and duration of action. Insulin regimens can be tailored to a patient's lifestyle.

6.2.1 Short-Acting Insulins

The short-acting insulins have fast onset (within 30 minutes) and short duration (less than 8 hours).

Lispro (Aspart) Has the fastest onset and shortest duration of all the insulins. Lispro is often injected 15 to 20 minutes before meals.

Regular Insulin Starts working within 30 minutes and is active about 5 to 8 hours. Buffered regular insulin often is used in insulin pumps.

Important Concept

Lispro provides patients who have diabetes more flexibility with meals than is possible with intermediate- or long-acting insulins.

6.2.2 Intermediate-Acting Insulins

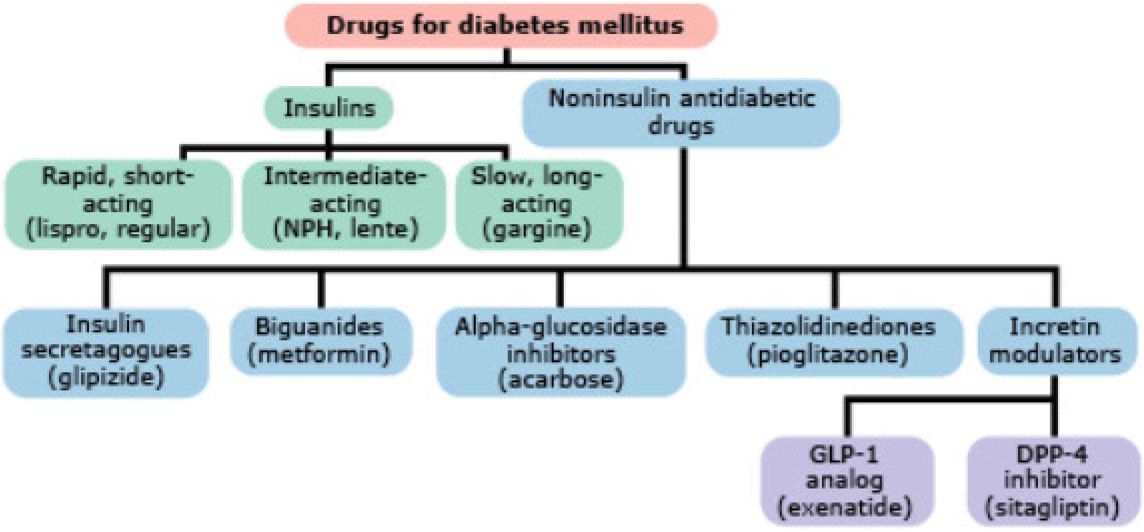
The intermediate-acting insulins include the following:

- Isophane
- Lente
- NPH (neutral protamine Hagedorn)
- Zinc suspension

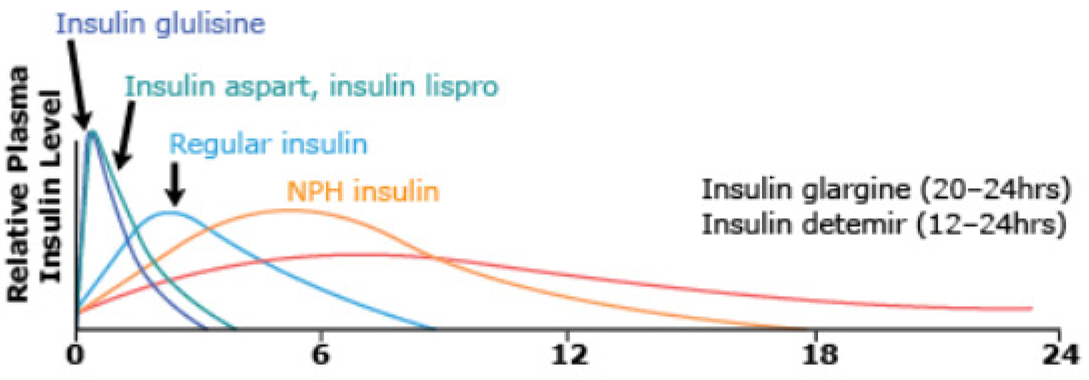
These insulins start working within 1 to 3 hours and are active for 16 to 24 hours.

6.2.3 Long-Acting Insulins

The long-acting insulins are active for 24 hours or more and include glargine (Lantus), detemir (Levemir), and ultra lente. Long-acting insulins are good at preventing the "dawn phenomenon," discussed below.


Drugs for diabetes mellitus
Insulins
Noninsulin antidiabetic drugs
Rapid, short-acting (lispro, regular)
Intermediate-acting (NPH, lente)
Slow, long-acting (gargine)
Insulin secretagogues (glipizide)
Biguanides (metformin)
Alpha-glucosidase inhibitors (acarbose)
Thiazolidinediones (pioglitazone)
Incretin modulators
GLP-1 analog (exenatide)
DPP-4 inhibitor (sitagliptin)

▲ **Figure 9-6.2A** Drugs for Type 2 Diabetes



▲ **Figure 9-6.2B** Onset and Duration of Insulin and Insulin Analogs

6.2.4 Islet Cell Transplantation

Islet cell transplantation is the transplantation of isolated islet cells from a donor pancreas into a recipient who has diabetes (usually type 1). The cells are usually infused into the liver. Although so far only a small fraction of patients with diabetes have received islet cell transplants, this option provides the potential for patients with type 1 diabetes to recover to the extent that they no longer need insulin therapy.

6.2.5 Somogyi Effect

The Somogyi effect is a problem often seen with patients on long-acting insulin therapy. The typical clinical scenario is low blood sugars in the middle of the night (2–3 a.m.). The cause is the release of counter-regulatory hormones (cortisol, epinephrine, glucagon, growth hormone) that overcome the effect of the long-acting insulin, leading to high blood sugar levels by dawn. The Somogyi effect usually can be prevented by a bedtime snack, which reduces the stimulus for the counter-regulatory hormones.

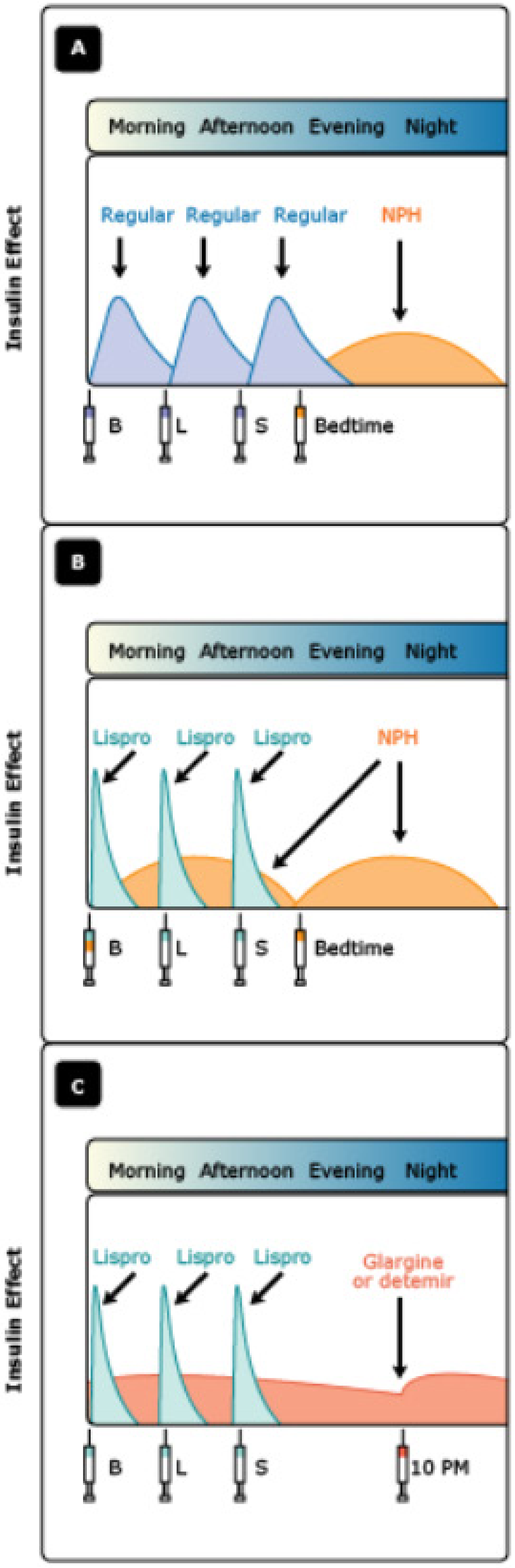
6.2.6 Dawn Phenomenon

The dawn phenomenon is caused by the normal physiologic peak of counter-regulatory hormones about dawn. In patients with diabetes, the effect of insulin (especially intermediate-acting) may be fading by dawn, leading to high blood sugar levels. The dawn phenomenon is minimized by the use of long-acting insulin (e.g., glargine) or by insulin pumps.

6.2.7 Insulin Overdose

Insulin overdose can happen because of the inadvertent or intentional administration of excessive amounts of insulin. Initial symptoms often include sympathetic effects such as tachycardia, sweating, and nausea, which are reflections of the release of counter-regulatory hormones to raise blood sugar. Severe overdose can lead to profound hypoglycemia, convulsions, tremors, and even death. Insulin also causes cells to take up potassium and magnesium, so hypokalemia and hypomagnesemia can be seen in insulin overdose.

Standard therapy is to have the patient, if able, drink a sweetened beverage or eat hard candy to provide a quick source of glucose. More severe overdoses can require urgent medical therapy, including the administration of intravenous dextrose (or intramuscular glucagon as an alternative), potassium, and magnesium.


A
Morning Afternoon Evening Night
Insulin Effect
Regular
Regular
Regular
NPH
B
L
S
Bedtime
B
Morning Afternoon Evening Night
Insulin Effect
Lispro
Lispro
Lispro
NPH
B
L
S
Bedtime
C
Morning Afternoon Evening Night
Insulin Effect
Lispro
Lispro
Lispro
Glargine or detemir
B
L
S
10 PM

▲ **Figure 9-6.2C** Comparison of Diabetes Treatment Regimens

6.3 Oral Hypoglycemic Agents

Oral hypoglycemic agents include a variety of drugs used to treat type 2 diabetes. These work by different mechanisms, including increasing insulin release and enhancing the cellular ability to respond to insulin.

Important Concept

Oral hypoglycemics are used for type 2 and not type 1 diabetics. These agents address the insulin resistance of type 2 diabetes.

6.3.1 Sulfonylureas

The sulfonylureas stimulate insulin release from the islet cells of the pancreas. They work by inhibiting an ATP-dependent K^+ (K_{ATP}) channel. Inhibition of this channel depolarizes the cells and leads to more insulin release. The two most common sulfonylureas used in the United States are glyburide and glipizide.

The sulfonylureas have the potential for causing hypoglycemia due to excessive insulin release. Sulfonylureas also can promote weight gain, as insulin promotes the utilization of glucose and other metabolic compounds. Sulfonylureas also can cause hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Important Concept

The sulfonylureas are the only oral hypoglycemic agents that can commonly cause hypoglycemia. This is due to the mechanism of action involving more insulin release as opposed to facilitating better response to existing insulin.

6.3.2 Thiazolidinediones

The thiazolidinediones are drugs that enhance the uptake of fatty acids and glucose in adipose tissue, muscle, and liver cells. Drugs in this group activate a nuclear hormone receptor known as the peroxisomal proliferator-activated receptor-γ (PPAR-γ). There are a number of safety concerns with these drugs—the prototype drug troglitazone was taken off the market because of such concerns.

Pioglitazone Currently the most widely used thiazolidinedione in the United States. The side effect profile is superior to rosiglitazone. However, an increased risk of bladder cancer has been associated with chronic therapy. It is recommended that patients not remain on pioglitazone for more than one year, if possible.

Rosiglitazone Associated with an increased risk of cardiovascular disease and death. Many countries have withdrawn this drug. Rosiglitazone remains on the U.S. market but with severe restrictions on prescriptions.

Adverse Effects Other effects associated with pioglitazone and rosiglitazone include an increased risk of bone fractures, weight gain, and edema.

6.3.3 Metformin

Metformin increases glucose uptake and reduces gluconeogenesis in the liver. Metformin does not cause hypoglycemia and, in contrast to other oral hypoglycemics, tends not to promote weight gain.

The most serious side effect associated with metformin is lactic acidosis. Lactate is a substrate for gluconeogenesis; by inhibiting gluconeogenesis, lactate levels can potentially rise. This generally is of no consequence, because there are other routes to clear lactate. However, patients with renal impairment, liver failure, and chronic hypoxic respiratory disease are at high risk for lactic acidosis and should not receive metformin. Metformin typically is withheld prior to and during surgical procedures and radiologic studies (especially those using intravenous contrast).

Important Concept

The adverse-effect profile of metformin relative to other oral hypoglycemics is high yield. Metformin is unlikely to cause weight gain (in contrast to other hypoglycemics). However, metformin is the only oral hypoglycemic associated with lactic acidosis.

6.3.4 α-Glucosidase Inhibitors

α-Glucosidase inhibitors block enzymes involved in the intestinal digestion of carbohydrates. This slows intestinal carbohydrate absorption. The prototype drug is acarbose.

The adverse effects associated with acarbose are mostly annoying ones because of carbohydrate malabsorption, such as bloating, diarrhea, and flatulence.

6.3.5 Dipeptidyl Peptidase-IV Inhibitors

Dipeptidyl peptidase-IV (DPP-IV) inhibitors block DPP-IV, an enzyme that normally breaks down glucagon-like peptide-1 (GLP-1). GLP-1 inhibits glucagon release and increases postprandial insulin. Sitagliptin and saxagliptin are the DPP-IV inhibitors currently used.

The adverse-effect profile of the DPP-IV inhibitors has been extremely good although the drugs have not been around very long. There are case reports of pancreatitis with both sitagliptin and saxagliptin.

6.3.6 Incretin (GLP-1) Mimetics (Exenatide)

Incretin mimetics act like GLP-1, thereby inhibiting glucagon release and increasing postprandial insulin. Exenatide is the only incretin mimetic currently approved in the United States. Exenatide is injected subcutaneously, usually before meals. There is a potential association with pancreatitis.

7 Thyroid Disorder Therapy

Thyroid disorders are common. Hypothyroidism is typically treated by thyroid hormone replacement. Hyperthyroidism can be more difficult to treat, and there are multiple therapeutic options. Most thyroid disorders are primary (involving the thyroid gland) and only rarely a result of pituitary or hypothalamic problems.

7.1 Overview of Thyroid Hormone Actions

Thyroid hormones are crucial determinants of normal development. Deficiency of thyroid hormone during fetal development or infancy can lead to mental retardation and growth problems. Throughout life, thyroid hormones help to maintain metabolic homeostasis, affecting virtually every organ system.

7.1.1 Thyroid Stimulating Hormone (TSH)

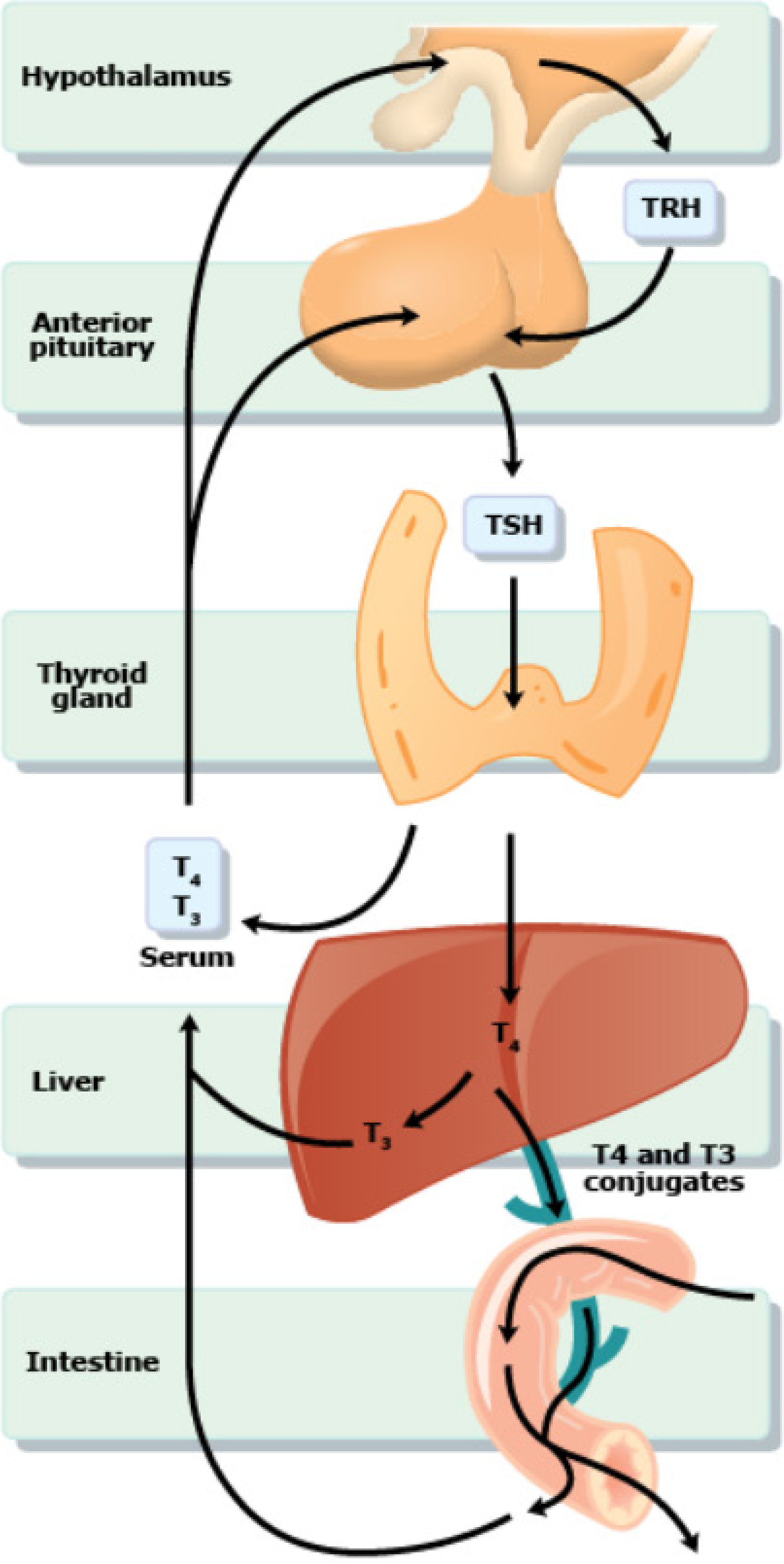
Thyroid stimulating hormone (TSH) is released by the anterior pituitary and stimulates the thyroid gland to produce thyroid hormones. Measurement of TSH is the screening test for thyroid function across all patient populations.

7.1.2 Thyroxine (T_4)

Thyroxine (T_4) contains four iodine molecules and is the main thyroid hormone released by the thyroid gland. T_4 is converted to T_3 (which has three iodine molecules) in the periphery. The most common form of thyroid hormone prescribed clinically is T_4. Plasma TSH and T_4 are typically followed in patients with thyroid illness. T_4 levels are approximately 20 times higher in the plasma than T_3.

7.1.3 Triiodothyronine (T_3)

Triiodothyronine (T_3) is the most biologically active form of thyroid hormone. Most T_3 is formed by peripheral conversion of T_4. There are prescriptions of T_3 that are used in some patients. However, T_3 is much more expensive than T_4 and is unnecessary for most patients with hypothyroidism.



▶ **Figure 9-7.1** Action of Thyroid Hormones

7.2 Hypothyroidism

Hypothyroidism is common in the United States and is more common in women and the old. The most common causes of hypothyroidism in the United States (in descending order of frequency) are:

- Autoimmune thyroiditis (e.g., Hashimoto thyroiditis)
- Thyroid gland ablation (by radioiodine or surgery)
- Iodine deficiency
- Drug toxicity (lithium, amiodarone)
- Pituitary dysfunction (lack of TSH)
- Hypothalamic dysfunction (very rare)

7.2.1 Symptoms of Hypothyroidism

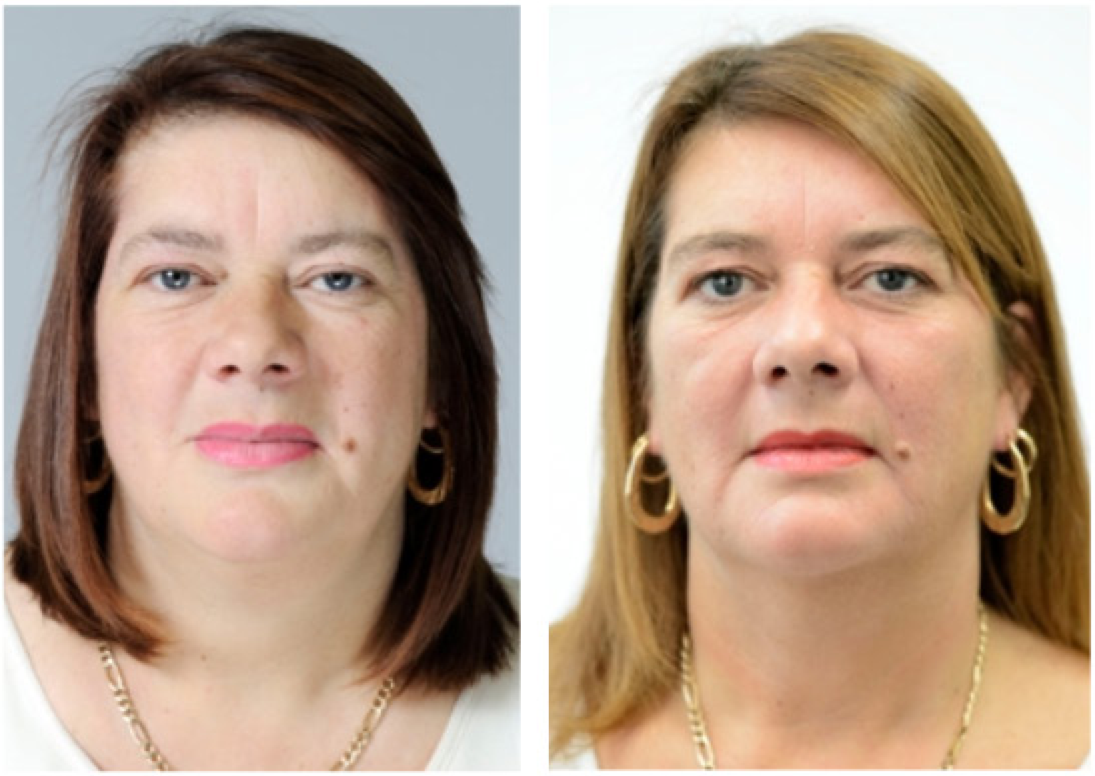
Hypothyroidism is associated with a variety of symptoms, many associated with sluggish metabolism:

- Weight gain
- Lethargy
- Depression
- Cold intolerance
- Myxedema (mucopolysaccharide-rich exudate that produces puffy skin and broadens facial features)
- Slow heart rate

Severe hypothyroidism can be life-threatening and is treated as a medical emergency.

7.2.2 Treatment of Hypothyroidism

Treatment of hypothyroidism is usually straightforward, consisting of thyroid hormone replacement with T_4. More complex cases may require T_3 to fine-tune the management of symptoms.



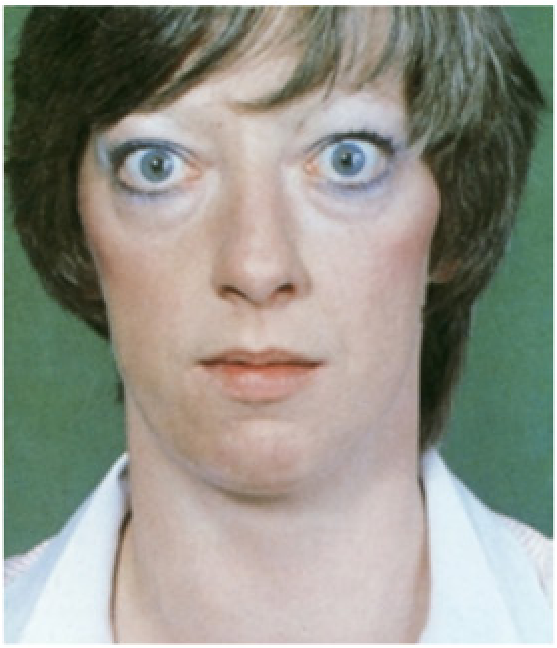
Dr. Kathy Johnson/Phototake, Inc.

▲**Figure 9-7.2** Myxedema

7.3 Hyperthyroidism

Hyperthyroidism is less common than hypothyroidism and can be difficult to treat. The most common causes of hyperthyroidism in the United States (in descending order of frequency) are:

- Graves disease (antibodies to TSH receptor)
- Thyroid adenoma
- Toxic multinodular goiter
- Thyroiditis (usually transient and eventually evolves into hypothyroiditis)
- Iodine excess
- Amiodarone
- TSH secreting tumor (rare)
- TRH secreting tumor (very rare)



Biophoto Associates/Science Source

▲**Figure 9-7.3A** Exophthalmia of Graves Disease

7.3.1 Symptoms of Hyperthyroidism

Hyperthyroidism is associated with a variety of symptoms, many associated with hyperactive metabolism:

- Tachycardia
- Nervousness, anxiety
- Sweating
- Weight loss
- Heat intolerance
- Myxedema (dry scaly skin often in legs, e.g., "pretibial" myxedma)
- Slow heart rate

7.3.2 Propylthiouracil and Methimazole

Propylthiouracil and methimazole are thyroid peroxidase inhibitors that block the formation of thyroid hormone in the thyroid gland. Propylthiouracil also inhibits the peripheral conversion of T_4 to T_3. Both drugs have a slow onset of action and may be used as main therapy or as a temporary measure before surgery or radioiodine therapy.

Propylthiouracil and methimazole are both associated with agranulocytosis. Propylthiouracil rarely has been associated with liver failure and carries an FDA black box warning for this effect.

7.3.3 Iodide (Nonradioactive)

Nonradioactive iodide (e.g., potassium iodide) is one of the older remedies for hyperthyroidism and is not commonly used in the United States. Iodide reduces thyroid gland size, fragility, and vascularity and is most commonly used as a temporary treatment to reduce thyroid gland size before surgery.

Adverse effects include an unpleasant, brassy taste with burning of the mouth and gums. Rare hypersensitivity reactions also can occur.

Important Concept

Myxedema is a confusing term which is applied to skin changes in both hypothyroidism and hyperthyroidism. Myxedema in hypothyroidism is dry, puffy skin, especially in the face. "Myxedema coma" refers to life-threatening hypothyroiditis. Myxedema in hyperthyroiditis from Graves disease is typically in the legs and is dry and scaly.

7.3.4 Radioactive Iodine

Radioactive iodine is very effective at completely ablating thyroid function. The patient is then maintained on thyroid hormone replacement. This treatment is absolutely contraindicated in pregnancy because it can destroy the fetal thyroid gland. Also, radioactive iodine is very expensive.

7.3.5 Surgery

Surgical removal of the thyroid gland is common. As with radioiodine ablation, the patient is then maintained on thyroid hormone replacement.

7.3.6 Adjunct Therapy for Hyperthyroidism

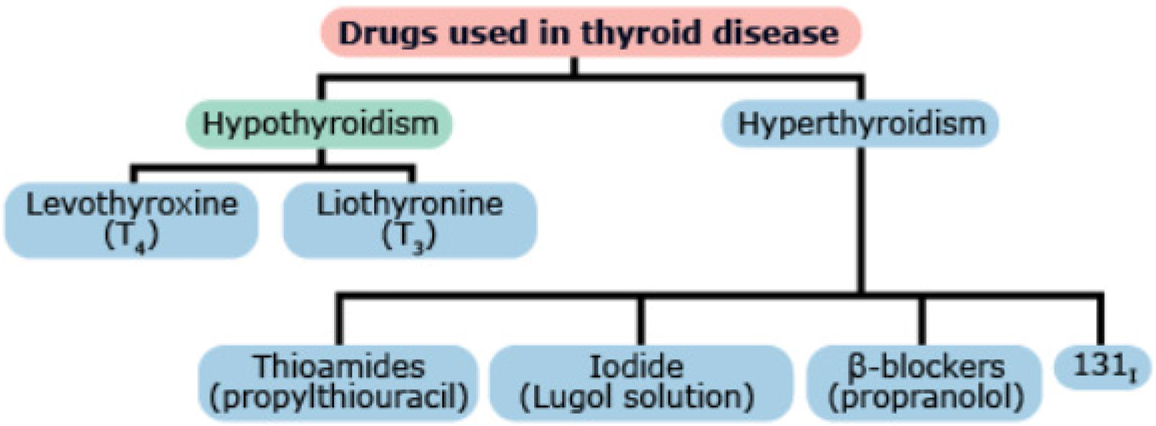
Adjunct therapy with β-blockers is often used in management of hyperthyroidism to reduce sympathetic symptoms, such as tachycardia, tremors, and anxiety. A nonselective β-blocker such as propranolol is typically preferred, because both β_1- and β_2-adrenergic receptors are upregulated in hyperthyroidism.

Life-threatening hyperthyroidism ("thyroid storm") is treated as a medical emergency. Acute measures, such as lowering body temperature rapidly, may be needed.

7.3.7 Treatment of Hyperthyroidism in Pregnancy

Management of hyperthyroidism in pregnancy is difficult. None of the common therapies are ideal. Propylthiouracil and methimazole are both category D in pregnancy (significant evidence of possible harm but the benefit may outweigh the risks). Propylthiouracil is generally preferred in the first trimester. Methimazole is preferred in the second and third trimesters.

Radioiodine is to be avoided completely due to the risk of destroying the fetal thyroid gland. Surgery is possible (especially in second trimester) but carries risks to the fetus such as exposure to anesthetics. Potassium iodide is category D because of the risk of neonatal goiter.



▲**Figure 9-7.3B** Thyroid Drugs

CHAPTER 10 Anticoagulant, Antiplatelet, and Thrombolytic Drugs

1 Anticoagulants

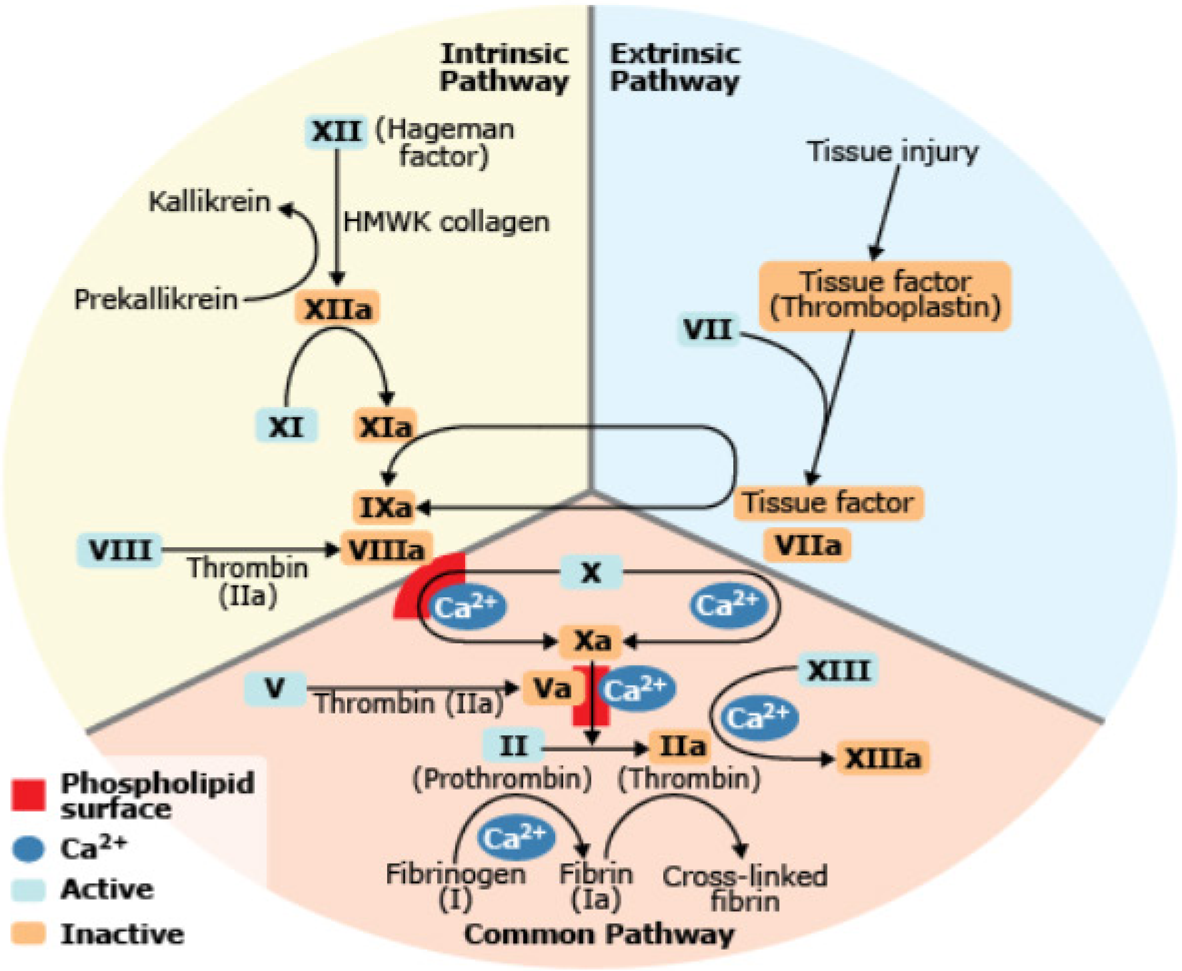
Anticoagulants are a commonly prescribed class of medications used to treat thromboembolic disorders. Although these drugs can be life-saving, they carry significant risk of adverse effects. The dominant anticoagulants are warfarin and the heparins; however, a number of newer anticoagulants have been introduced in the last decade.

1.1 Overview of Anticoagulants

Anticoagulants are used both as treatment for abnormal blood clotting and as prophylaxis for patients at risk for clotting complications. The most common indications for anticoagulant therapy are *deep venous thrombosis* (in femoral veins), *atrial fibrillation, mechanical heart valves,* and *inherited clotting disorders*.

1.1.1 Clotting Cascade

Basic knowledge of the clotting (coagulation) cascade is helpful in understanding anticoagulants. This cascade is divided into the *intrinsic pathway* and *extrinsic pathway*, with overlap between the two pathways in the *common pathway*. Factors VIII and IX are unique to the intrinsic pathway, while factor VII is unique to the extrinsic pathway. Factors II, V, and X are in the common pathway.


Intrinsic Pathway
Extrinsic Pathway
XII (Hageman factor)
HMWK collagen
Kallikrein
Prekallikrein
XIIa
XI
XIa
IXa
VIII
Thrombin (IIa)
VIIIa
Tissue injury
Tissue factor (Thromboplastin)
VII
Tissue factor
VIIa
X
Ca2+
Ca2+
Xa
V
Thrombin (IIa)
Va
Ca2+
XIII
Ca2+
II
IIa
XIIIa
(Prothrombin)
(Thrombin)
Ca2+
Fibrinogen (I)
Fibrin (Ia)
Cross-linked fibrin
Common Pathway
Phospholipid surface
Ca2+
Active
Inactive

▲**Figure 10-1.1** Clotting Cascade

USMLE® Key Concepts

For Step 1, you must be able to:

- Describe the mechanism of action of anticoagulants, thrombolytic, and anti-platelet drugs.
- Explain how anticoagulant therapy with heparin and warfarin is monitored and identify the antidotes for these two drugs.
- Describe the clinical indications for anticoagulants, thrombolytic, and anti-platelet drugs.
- List the adverse effects associated with anticoagulants, thrombolytic, and anti-platelet drugs.

1.1.2 Prothrombin Time (PT) and International Normalized Ratio (INR)

Prothrombin time (PT) is a laboratory test that assesses the function of the extrinsic and common pathways. Calcium and tissue factor are added to citrated blood, and the time to clot is measured. The prothrombin time is standardized by the International Normalized Ratio (INR). *An INR of 1 is normal; values above 1 indicate anticoagulation.* The INR is commonly used to follow patients on warfarin therapy, typically with a target INR somewhere between 2.5 and 3.5, depending on the indication for warfarin therapy.

1.1.3 Partial Thromboplastin Time (PTT)

The partial thromboplastin time (PTT) assesses the intrinsic and common pathways. PTT is commonly used to follow patients on heparin therapy.

1.2 Inherited Clotting Disorders

Several inherited clotting disorders are known. In some cases, these genetic variants result in greatly increased risk of thromboembolism.

1.2.1 Factor V Leiden

Factor V Leiden is a genetic variant of factor V that is more prone to clotting. This is an autosomal dominant disorder with incomplete penetrance. Patients homozygous for the factor V Leiden have very high risk for thromboembolism. This risk is further increased by cigarette smoking.

1.2.2 Prothrombin Variant

The prothrombin G20210A is a genetic variant that carries increased risk of thromboembolism. As with factor V Leiden, patients homozygous for the prothrombin variant have very high risk for thromboembolism.

1.2.3 Protein C and S Deficiencies

Deficiencies of the endogenous anticoagulants protein C and S are much less common than factor V Leiden or prothrombin variants. These variants carry much higher risk of thromboembolism than factor V Leiden or prothrombin G20210A, often presenting with clotting disorders in childhood.

1.3 Anticoagulant Therapy

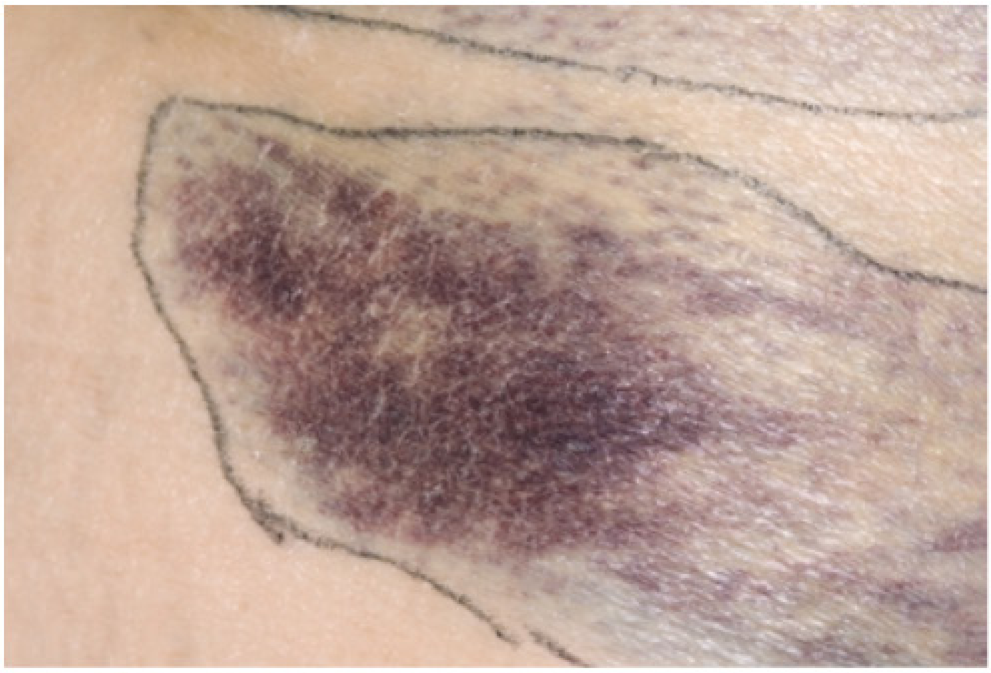
The dominant anticoagulants are heparin and warfarin, although more drugs have become available in the last decade. Keep in mind that *anticoagulation is not the same as antiplatelet therapy* (as with aspirin or clopidogrel).

1.3.1 Overview

Anticoagulants are used to treat and prevent thromboembolism. *Anticoagulants do not break down preexisting clots* (thrombolytics are needed for that), but can prevent formation of new clots.

1.3.2 Unfractionated Heparin

Unfractionated heparin is not a single molecule, but instead a complex mixture of large, water-soluble polysaccharide molecules of varying size, mostly 15–20 kilodalton. Heparin is not absorbed following oral administration and *must be given parenterally* (usually by subcutaneous or intravenous administration). Heparin therapy is optimized by monitoring PTT and making heparin dose adjustments based on the PTT values.



Dr. P. Marazzi/Science Source

▲**Figure 10-1.3** Heparin-Induced Skin Necrosis

Mechanism of Action Heparin increases the activity of *antithrombin III,* an endogenous molecule that inactivates thrombin (factor II) and factor Xa.

Clinical Uses Heparin is commonly used to prevent thromboembolism, especially in the hospital setting. It is used in *cardiac bypass surgery* to prevent clots in the extracorporeal circuit. Heparin provides rapid anticoagulation, which is especially useful in preventing further clotting in patients with *deep venous thrombosis* or *pulmonary embolism*. Heparin is also a good choice for anticoagulation in pregnancy because it does not cross the placental barrier.

Adverse Effects Heparin's major adverse effect is bleeding. Less common side effects are heparin-induced *thrombocytopenia* (which may paradoxically present as clotting) and a rare immune reaction of skin necrosis at the site of injection. Due to its large molecular size and charge, heparin does not cross the placenta and is thus much safer than warfarin in pregnancy.

1.3.3 Low Molecular Weight Heparins and Related Drugs

The low molecular weight heparins include the prototype drug enoxaparin, and fondaparinux, a related drug that specifically inhibits factor Xa.

Enoxaparin Like heparin, enoxaparin enhances the activity of *antithrombin III*. It is not absorbed orally and is given by subcutaneous injection. Enoxaparin does not generally increase PT and PTT, but can be monitored by anti-factor Xa levels. Enoxaparin is less likely to cause heparin-induced thrombocytopenia than unfractionated heparin. Like unfractionated heparin, enoxaparin can be used in pregnancy.

Fondaparinux This agent is a synthetic pentasaccharide chemically related to low molecular weight heparin. Fondaparinux is a *direct factor Xa inhibitor*.

1.3.4 Warfarin

Warfarin remains the most commonly used oral anticoagulant despite having a host of potential adverse effects.

Mechanism of Action Warfarin inhibits vitamin K recycling by inhibition of the vitamin K epoxide reductase complex subunit 1 (VKORC1; often shortened to VKOR for convenience), thereby reducing the effect of the vitamin K–dependent clotting factors II, VII, IX, and X. Warfarin is antagonized by high doses of vitamin K, which is one antidote for excessive warfarin.

Clinical Uses Warfarin is used for long-term anticoagulation for patients who are high risk for thromboemboli (those with inherited clotting defect, mechanical heart valves, or atrial fibrillation), patients with known deep venous thrombosis, and patients with large anterior myocardial infarction. Warfarin therapy is optimized by following the prothrombin time (PT), usually standardized as the INR. The target INR for warfarin therapy is usually between 2.5 and 3.5, depending on the clinical indication.

Drug and Diet Interactions Warfarin has a prodigious number of drug and diet interactions. Warfarin is predominantly metabolized by cytochrome P450 2C9 (CYP2C9). Drugs that inhibit CYP2C9 increase warfarin levels and increase risk of excessive anticoagulation, including:

- Cimetidine
- Trimethoprim-sulfamethoxazole
- Ketoconazole

Patients who are on warfarin and a CYP2C9 inhibitor like trimethoprim-sulfamethoxazole typically require *lower* doses of warfarin to achieve target level of anti-coagulation.

Conversely, drugs that induce (increase) CYP2C9 expression reduce warfarin levels. These include:

- Rifampin
- Carbamazepine
- Phenobarbital
- Phenytoin
- St. John's wort

Patients who are on warfarin and a CYP2C9 inducer like rifampin typically require *higher* doses of warfarin to achieve target level of anti-coagulation.

Diets high in vitamin K reduce warfarin effect. Patients are often advised to maintain a consistent level of dietary vitamin K to avoid fluctuations in warfarin effect.

Pharmacogenetics The genes for CYP2C9 (warfarin metabolism) and VKOR (pharmacodynamic target for warfarin) show clinically significant variation. Several relatively common mutations in the gene for CYP2C9 (especially the *2 and *3 variants) lead to decreased ability to metabolize warfarin. Patients with these variants should get lower doses of warfarin.

A variant in the promoter for the VKOR gene reduces protein expression and thereby increases warfarin's ability to inhibit vitamin K activity. Patients with the VKOR variant should also get lower warfarin doses.

Dosage information is available on websites that have algorithms for estimating optimal warfarin dosing based on age, gender, ethnicity, CYP2C9 and VKOR genetics, concomitant medications, and indication for warfarin therapy.

Adverse Effects The main adverse effect of warfarin is bleeding, which can manifest as gastrointestinal or cerebral hemorrhage. A rare side effect is skin necrosis, an idiosyncratic side effect that appears early in warfarin therapy. The therapeutic effect of warfarin is dependent on decreased production of clotting factors, which can take several days.

One recognized problem early in warfarin therapy is that protein C and protein S (endogenous "anti-coagulants") are also vitamin K-dependent and have short half-lives. Therefore, deficiency of proteins C and S relative to the pro-clotting factors (II, VII, IX, and X) early in warfarin therapy can lead to a transient period in which patients are actually prone to increased clotting. Patients are often started on heparin as a "bridge" together with warfarin to prevent this type of complication in the early phase of warfarin therapy.

Warfarin overdose can be managed by infusion of fresh frozen plasma (FFP, which provides pre-formed clotting factors) or high-dose vitamin K. FFP is indicated in severe overdoses with hemorrhage.

Warfarin and Pregnancy Warfarin is teratogenic and contraindicated in pregnancy (category X). Heparins (unfractionated or low-molecular weight) are the safer alternatives.

1.3.5 Argatroban

Argatroban is a direct thrombin inhibitor derived from arginine that is predominantly used in the hospital setting. Argatroban is metabolized by the liver and may be used in patients with renal failure. No antidote is available for argatroban.

1.3.6 Lepirudin

Lepirudin is a direct thrombin inhibitor derived from a compound isolated from the medicinal leech. Lepirudin is cleared by the kidneys and avoided in patients with renal failure. Lepirudin was removed from the U.S. market in summer of 2012 and may not return to clinical use.

1.3.7 Dabigatran

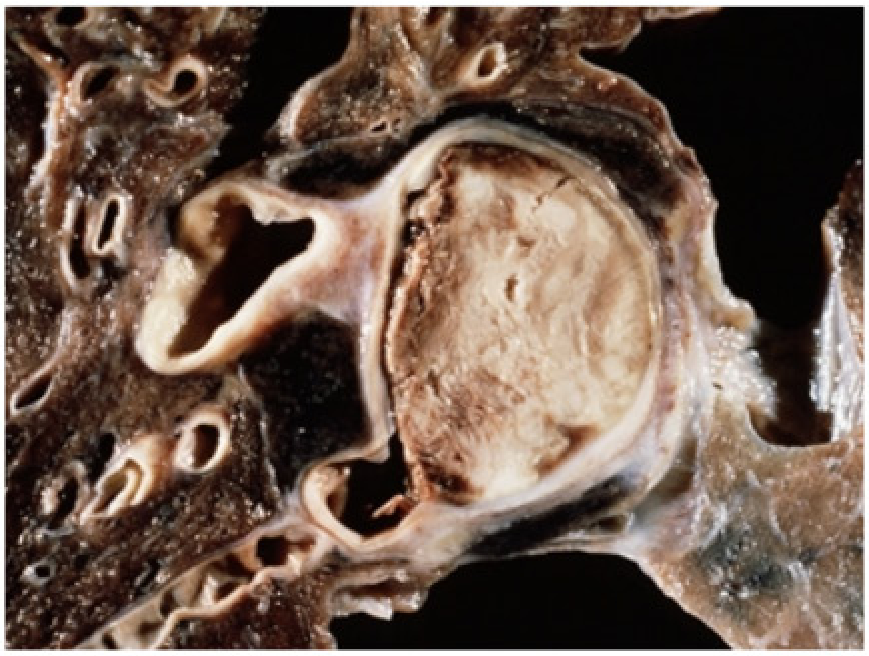
Dabigatran is an oral anticoagulant originally projected to replace warfarin. Dabigatran is used for many of the same clinical indications as warfarin; however, bleeding complications have slowed clinical use. About 10 percent of patients suffer bleeding effects, with gastrointestinal bleeding being especially common. Dabigatran should be avoided in renal failure patients. There is currently no antidote.

2 Thrombolytics

Thrombolytics are drugs used to break down blood clots. The effectiveness of these agents is heavily mediated by how quickly they are administered.

2.1 Overview of Thrombolytics

The fibrinolytic system dissolves intravascular clots as a result of the action of plasmin, an enzyme that digests fibrin. Thrombolytics are given intravenously for emergency management of coronary thromboses, deep venous thromboses, pulmonary embolism, and thromboembolic strokes. For the use of thrombolytics in strokes, proper diagnosis of the underlying cause of the stroke is crucial, given that use of thrombolytics in hemorrhagic stroke is contraindicated due to risk of accelerating the bleeding.

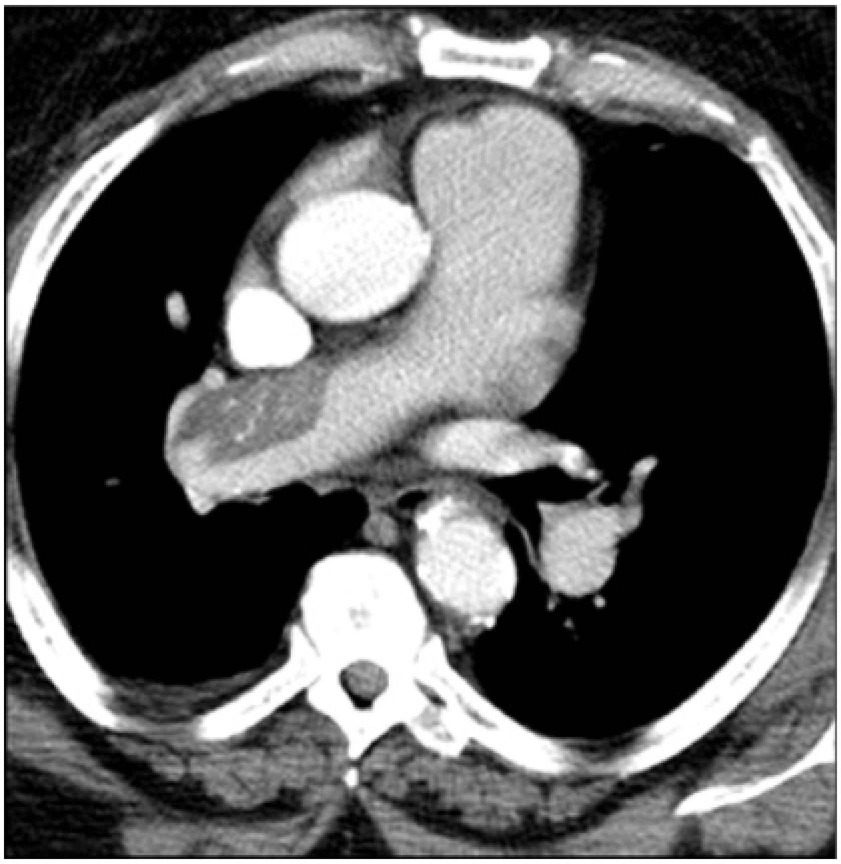


CNRI/Science Source

▲**Figure 10-2.1** Pulmonary Embolus

2.2 Tissue Plasminogen Activator (Alteplase, Reteplase, Tenecteplase)

Tissue plasminogen activator (tPA) is an enzyme that catalyzes the conversion of plasminogen to plasmin. Plasmin then catalyzes the breakdown of fibrin. Three recombinant forms of tPA are marketed (alteplase, reteplase, tenecteplase), each with indications for treatment of acute myocardial infarctions.



Living Art Enterprises/Science Source

▲**Figure 10-2.2** Thrombolysis of Pulmonary Embolus by tPA

2.3 Streptokinase

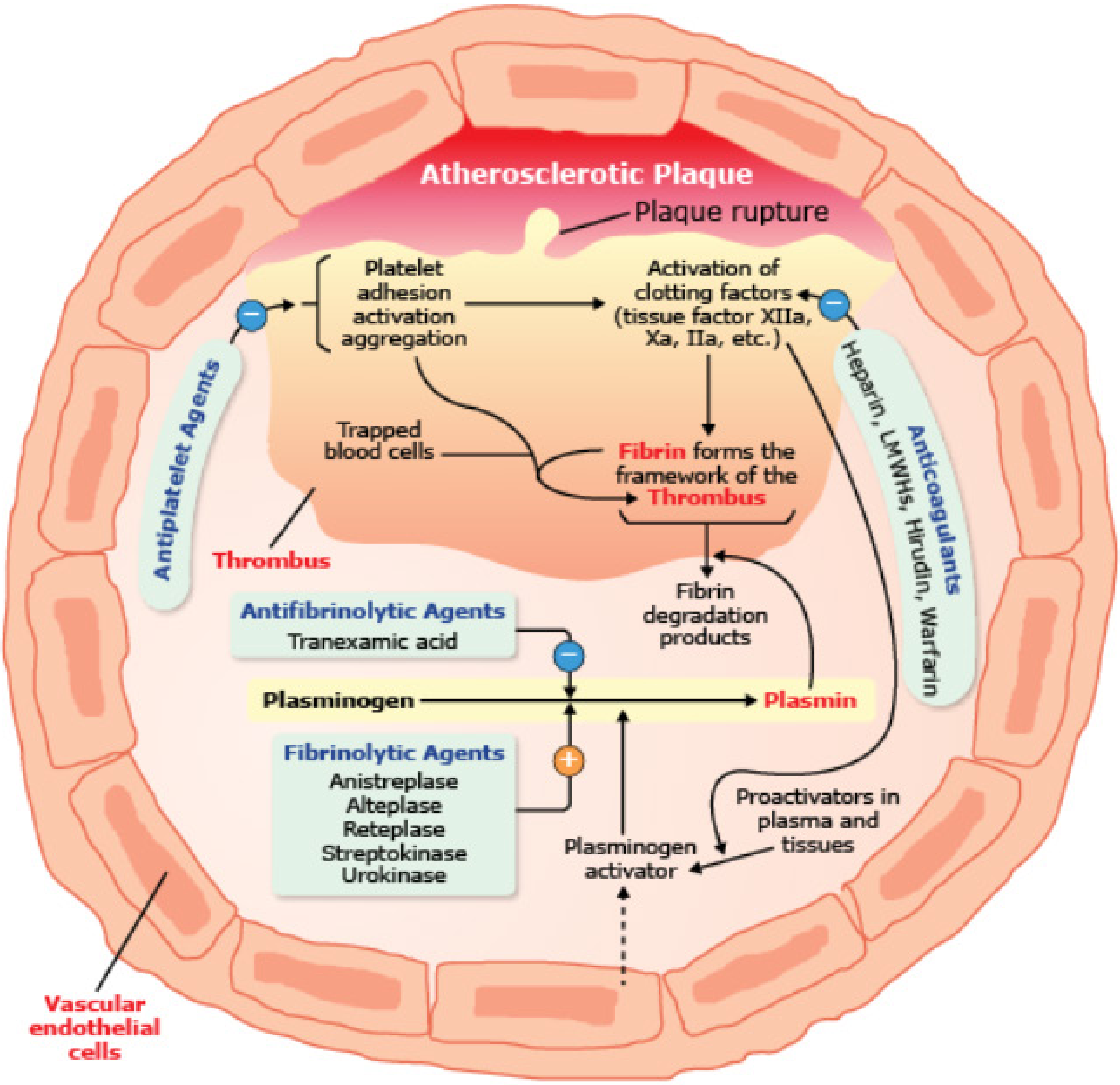
Streptokinase is an enzyme found in streptococci. Like tPA, streptokinase catalyzes the conversion of plasminogen to plasmin. Streptokinase's main limitation is that it is recognized as a foreign protein, with antibodies developing against it. Streptokinase should not be used four days or more after a previous injection due to risk of allergic reaction.

2.4 Adverse Effects

The major adverse effects of thrombolytics are bleeding and hemorrhage. The risk of hemorrhage is increased when thrombolytics are used with heparin. Thrombolytic action can be reversed with tranexamic acid (anti-fibrinolytic agent) or fresh frozen plasma.

Thrombolytics are contraindicated in clinical situations with a high risk of hemorrhage. These include:

- Surgery planned within 10 days
- Serious gastrointestinal bleed within last 3 months
- Active bleeding or hemorrhagic disorder
- Previous cerebrovascular accident
- Aortic dissection


Atherosclerotic Plaque
Plaque rupture
Platelet adhesion activation aggregation
Activation of clotting factors (tissue factor XIIa, Xa, IIa, etc.)
Antiplatelet Agents
Anticoagulants
Heparin, LMWHs, Hirudin, Warfarin
Trapped blood cells
Fibrin forms the framework of the Thrombus
Thrombus
Fibrin degradation products
Antifibrinolytic Agents
Tranexamic acid
Plasminogen
Plasmin
Fibrinolytic Agents
Anistreplase
Alteplase
Reteplase
Streptokinase
Urokinase
Proactivators in plasma and tissues
Plasminogen activator
Vascular endothelial cells

▲**Figure 10-2.3** Fibrinolytic System

3 Antiplatelet Drugs

Antiplatelet drugs are widely used to reduce risk of myocardial infarction and other complications of atherosclerosis.

3.1 Overview of Platelet Function

Platelets provide the initial hemostatic plug at sites of vascular injury. Platelets are generally more active in arteries compared to veins. Platelet thrombosis plays a pathologic role in myocardial infarction, stroke, and peripheral vascular disease.

3.2 Aspirin

The prototype antiplatelet agent is aspirin, which blocks production of thromoboxane A2 by permanently inhibiting cyclooxygenase-1 (COX-1) in platelets. An 81 mg daily dose of aspirin ("baby aspirin") is widely used to lower risk of myocardial infarction. The main adverse effects of aspirin are gastrointestinal upset and bleeding.

3.3 Platelet Adenosine Diphosphate (ADP) Receptor Antagonists

Clopidogrel (Plavix) and ticlopidine (Ticlid) block the actions of ADP on platelets. These drugs are an alternative to aspirin for patients. The rare adverse effects are severe neutropenia and thrombocytopenia, which are more common with ticlopidine. Clopidogrel is currently much more widely used than ticlopidine.

3.4 Glycoprotein IIb/IIIa Inhibitors

Glycoprotein IIb/IIIa is a fibrinogen receptor/integrin on platelets. The prototype inhibitor of glycoprotein IIb/IIIa is abciximab, a Fab fragment of a humanized monoclonal antibody directed against the IIb/IIIa receptor. A similar drug is eptifibatide. The IIb/IIIa inhibitors provide rapid anti-platelet effect and are used in acute coronary syndromes, often in conjunction with coronary artery procedures. The major adverse effect is bleeding.

Review Questions Chapters 9–10

The following vignette applies to questions 1 and 2.

A 55-year-old male presents with fatigue, decreased libido, worsening impotence, and progressive loss of facial and pubic hair. He underwent a hypophysectomy for a pituitary tumor six weeks ago. Physical examination reveals gynecomastia and bilateral testicular atrophy.

1. Pharmacotherapy with which of the following agents is *most appropriate* for long-term management of his sexual symptoms?

A. Thyroid stimulating hormone
B. Luteinizing hormone (LH)
C. Testosterone undecanoate
D. Follicle-stimulating hormone (FSH)
E. Chorionic gonadotropin

2. For this same patient, the presence of what coexisting disease would be a contraindication to the therapy you indicated above?

A. Emphysema
B. Prostate carcinoma
C. Indirect inguinal hernia
D. Renal insufficiency
E. Hypothyroidism

The following vignette applies to questions 3 and 4.

A 16-year-old female is found unconscious in a restroom. An empty insulin needle on the ground near her looks as if it were injected. She is wearing a wristband identifier that indicates she has type I (juvenile-onset) diabetes mellitus. Paramedics are notified and after they arrive they note that the patient has a pulse of 100 bpm, blood pressure of 90/45 mmHg, and is responsive only to painful stimuli. Other aspects of the physical examination are unremarkable.

3. Which of the following laboratory values *most likely* would represent this patient?

A. Serum sodium 170 mEq/L (normal 136–145)
B. Serum glucose 1,250 mg/dL (fasting normal 70–110)
C. Serum sodium 115 mEq/dL
D. Hematocrit 18% (normal 36–46)
E. Serum glucose 25 mg/dL

4. What agent given *intravenously* would be indicated in this scenario?

A. Packed erythrocytes
B. Norepinephrine
C. Dextrose solution
D. Insulin
E. Sodium bicarbonate solution

Chapters 9–10 Review Questions

The following vignette applies to questions 5 and 6.

A 55-year-old male presents to the emergency room with recent onset of crushing substernal chest pain radiating down his left arm. He undergoes multi-vessel coronary artery bypass grafting and is maintained on heparin for one week. He presents again to the emergency room complaining of weakness and mild chest pain. His stool guaiac was previously negative, but is now 4+.

5. What laboratory parameter is *most likely* markedly elevated in this patient?

A. Lupus anticoagulant
B. D-dimer test
C. Activated partial thromboplastin time
D. Factor VIII inhibitor screen
E. Platelet count

6. For this same patient, which of the following drugs was *most likely* first given to counteract the bleeding?

A. Protamine sulfate
B. Vitamin K
C. Recombinant factor VIII
D. ε-Aminocaproic acid
E. Arginine vasopressin

The following vignette applies to questions 7 and 8.

A 70-year-old man is recovering from extensive orthopedic surgeries to repair lower extremity fractures associated with a motor vehicle accident. Following the surgeries, the patient is immobile for an extended period. To prevent deep venous thrombosis, the patient is started and then maintained on anticoagulation therapy with heparin. However, despite this, he becomes acutely dyspneic, which develops into respiratory distress.

7. Which of the following scenarios would be the *strongest* contra-indication to therapy to breakdown blood clots in this patient?

A. History of iron-deficiency anemia
B. Severe gastrointestinal bleed within the last month
C. History of myocardial infarction eight months ago
D. Planned additional orthopedic surgery in one month
E. History of aspirin ingestion within the last week

8. Which of the following medications could be used long-term as an *orally* administered anti-coagulant?

A. Unfractionated heparin
B. Enoxaparin
C. Lepirudin
D. Argatroban
E. Dabigatran

Review Answers Chapters 9–10

1. The correct answer is C. Testosterone undecanoate. This is a case of acquired (secondary) hypogonadism. In this patient, the hypophysectomy resulted in decreased levels of FSH and LH and a decreased serum testosterone level. Testosterone replacement using a testosterone ester such as testosterone undecanoate, either by transdermal patch, periodic depot injection, or pill form, generally will produce an increase in mood, libido, energy, and sexual function. Therapy with LH or FSH, although sometimes used for the treatment of male infertility, is not appropriate for this patient, who will need long-term therapy.

2. The correct answer is B. Prostate carcinoma contraindicates therapy with testosterone, as testosterone may stimulate the growth of the prostate carcinoma. The prostate gland is very sensitive to testosterone, which is converted to dihydrotestosterone. The other conditions listed would not be predicted to be sensitive to testosterone therapy.

3. The correct answer is E. Serum glucose 25 mg/dL. The most likely scenario here is hypoglycemia secondary to insulin overdose, whether intentional or inadvertent. Diabetic ketoacidosis (DKA) also is a possibility, although there is no mention of "fruity" breath odor (from acetone) or Kussmaul respiration (gasping breathing), which would be associated with DKA. Note also that a serum glucose of 1,250 mg/dL would be unusually high for DKA and more likely would be seen with hyperglycemic hyperosmolar non-ketotic coma, which is seen more often in middle-aged or older patients with type 2 diabetes mellitus.

4. The correct answer is C. Dextrose solution is given rapidly and intravenously to treat hypoglycemia due to insulin overdose. This usually has rapid therapeutic benefit. There is no need for erythrocyte transfusion, norepinephrine, or sodium bicarbonate. In a patient with insulin overdose, giving further insulin would be unhelpful. If intravenous access is not possible, then glucagon, one of the "counter-regulatory hormones" that opposes the effects of insulin, can be given intramuscularly to treat hypoglycemia secondary to insulin overdose. The effect is somewhat slower than intravenous dextrose infusion but may be indicated if intravenous access is difficult.

5. The correct answer is C. Activated partial thromboplastin time (aPTT) is most affected by heparin administration as is the thrombin time (not listed as one of the choices). The aPTT assesses the intrinsic clotting pathway. Lupus anticoagulant would not be commonly expected with heparin therapy. D-dimer, factor VIII inhibitor, and platelet count would not be expected to be elevated because of heparin.

6. The correct answer is A. Protamine sulfate binds to heparin to form a stable complex that has no anticoagulant activity (an example of physical antagonism). Vitamin K would reverse the effects of warfarin (Coumadin) but not heparin. Recombinant factor VIII would be used for a patient with hemophilia A. ε-Aminocaproic acid inhibits fibrinolysis and has been used to reduce bleeding in hemophiliacs. Arginine vasopressin is sometimes used to stop bleeding esophageal and gastric varices in patients with portal hypertension.

Chapters 9–10 Review Answers

7. The correct answer is B. Serious gastrointestinal bleed within last month. t-PA or other thrombolytic therapy is contraindicated in situations in which risk of hemorrhage is great. These include surgery within 10 days, serious gastrointestinal bleeding within three months, active bleeding or hemorrhagic disorder, previous cerebrovascular accident or active intracranial process, and aortic dissection.

8. The correct answer is B. Dabigatran is an oral anticoagulant that works as a direct thrombin inhibitor. The other agents listed cannot be given orally and must be given parenterally (subcutaneous and/or intravenous administration).

CHAPTER 11

Drugs for Disorders of Connective Tissue and the Musculoskeletal System

1 Therapies for Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune chronic inflammatory disorder that classically affects the small joints in the hand and feet. Rheumatoid arthritis is more common in women than men and occurs most frequently between the ages of 40 and 60. Therapies for rheumatoid arthritis are aimed at managing the acute symptoms but also preventing permanent bone erosion and joint damage.

1.1 Therapeutic Approach to Rheumatoid Arthritis

Rheumatoid arthritis is often initially managed by NSAIDs and steroids. However, *disease-modifying antirheumatic drugs (DMARDs)* are often needed. Current recommendations are to use these drugs fairly early to prevent long-term joint complications.

1.2 NSAIDs

NSAIDs such as aspirin, ibuprofen, and naproxen can relieve the pain and reduce the inflammation of rheumatoid arthritis. NSAIDs can be quite effective in managing the symptoms of rheumatoid arthritis but in general do not modify the disease course.

1.3 Corticosteroids

Corticosteroids such as prednisone *reduce pain and inflammation* and *slow joint damage*. However, corticosteroids, particularly when used at higher doses for extended periods of time, are associated with a number of adverse *Cushingoid effects,* including *osteoporosis,* weight gain, and *insulin resistance*. Corticosteroids are often used to relieve acute symptoms of rheumatoid arthritis, with the goal of tapering off the medication.

1.4 Disease-Modifying Antirheumatic Drugs (DMARDs)

DMARDs include a range of therapies that *tackle the underlying autoimmune processes* of rheumatoid arthritis. The goals of DMARD therapy is to *slow the progression of disease* and protect joints and bone from permanent damage and deformity.

The DMARDs include methotrexate, hydroxychloroquine, gold salts, leflunomide/teriflunomide, penicillamine, and a group of drugs classified as biologics (infliximab, etanercept, adalimumab, and rituximab). The biologics tend to used for more severe disease and also carry greater risk of serious adverse effects (especially infections).

USMLE® Key Concepts

For Step 1, you must be able to:

- Explain the mechanism of action and adverse effects of agents used to treat rheumatoid arthritis.
- Describe the drugs used to manage acute and chronic gout and their adverse effects.
- List the medications and dietary management of osteoporosis.
- Identify the therapeutic indications and adverse effects of bisphosphonates and calcitonin.

1.4.1 Methotrexate

Methotrexate is a first-line DMARD that works by a *cytotoxic effect* on lymphocytes. It has a *suppressive action on bone marrow* which increases risk of infections. Unlike the use of methotrexate in cancer therapy, leucovorin "rescue" is very rarely needed when methotrexate is used as a DMARD.

1.4.2 Hydroxychloroquine

Hydroxychloroquine is used both for *malaria* treatment (although not as commonly as chloroquine or mefloquine) and also to treat autoimmune disorders such as *lupus* and *rheumatoid arthritis*. The exact mechanism of action for treatment of autoimmune disease is not known, although the drug reduces rheumatoid factor and other acute phase reactants.

Similar to other quinine-related anti-malarials (chloroquine, mefloquine, primaquine), hydroxychloroquine can trigger *hemolytic anemia* in patients with glucose-6-phosphase dehydrogenase (G6PD) deficiency. Long-term hydroxychloroquine therapy carries risk of eye damage due to *macular* and *corneal deposits*. The risk of eye damage increases with higher cumulative doses that occur over years of therapy. Regular ophthalmic examinations are recommended.

1.4.3 Gold Salts (Auranofin, Aurothioglucose)

Gold salts are an infrequently used group of DMARDs. The mechanism of action is not clearly understood. The expense associated with gold salts limit their therapeutic use.

Common adverse effects are skin rash and mouth sores. Kidney injury and myelosuppression occur less commonly.

Memory Aid

All drugs classified as gold salts begin with the two letters *Au* (from Latin *aurum*), the two-letter abbreviation for the element gold ("Au do you want some gold?").

1.4.4 Leflunomide and Teriflunomide

Leflunomide is a DMARD that acts by inhibition of the mitochondrial *dihydroorotate dehydrogenase,* an enzyme needed for *de novo* synthesis of *pyrimidines*. The majority of the clinical effect is via the active metabolite teriflunomide, which received FDA approval in late 2012. Leflunomide is also used off-label for *treatment of BK virus* infection in solid organ recipients.

The most serious adverse effects of leflunomide and teriflunomide are *liver toxicity* and *myelosuppression,* either of which can be fatal. Patients on these agents are generally followed by regular monitoring of liver function tests and complete blood counts.

1.4.5 Penicillamine

Penicillamine *suppresses the function of T lymphocytes*. It is also a *chelator of heavy metals,* although this action is not important in its use as a DMARD.

The most common serious adverse effects of penicillamine are *bone marrow suppression, nephropathy,* and a *lupus-like syndrome*. The risk of lupus-like side effects are increased in patients who are "slow acetylators" (low activity of the enzyme *N*-acetyltransferase). There is also some cross-allergenicity between penicillin and penicillamine.

1.4.6 Infliximab (Remicade)

Infliximab is a mouse-human chimeric *monoclonal antibody* directed *against tumor necrosis factor-α* (TNF-α). Infliximab is used as a DMARD and also to treat other autoimmune disorders *(ankylosing spondylitis, psoriasis, Crohn disease,* and *ulcerative colitis)*.

Infliximab therapy carries risk of bone marrow suppression, with increased rate of serious infections (including *reactivation of hepatitis B* and *tuberculosis*), demyelinating central nervous system disorders, and lymphomas. Patients are typically tested for hepatitis B, hepatitis C, and HIV prior to initiating infliximab therapy.

1.4.7 Etanercept (Enbrel)

Etanercept is a biologic comprising the TNF receptor fused to human IgG fragment. Etanercept binds to and inhibits *TNF-α*.

The adverse effects of etanercept are similar to those of infliximab. Patients should be tested for hepatitis B, hepatitis C, and HIV prior to initiating therapy.

1.4.8 Adalimumab (Humira)

Adalimumab is a fully human *monoclonal antibody directed against TNF-α* used as a DMARD. Adverse effects are similar to those of infliximab and etanercept. Patients should be tested for hepatitis B, hepatitis C, and HIV prior to initiating therapy.

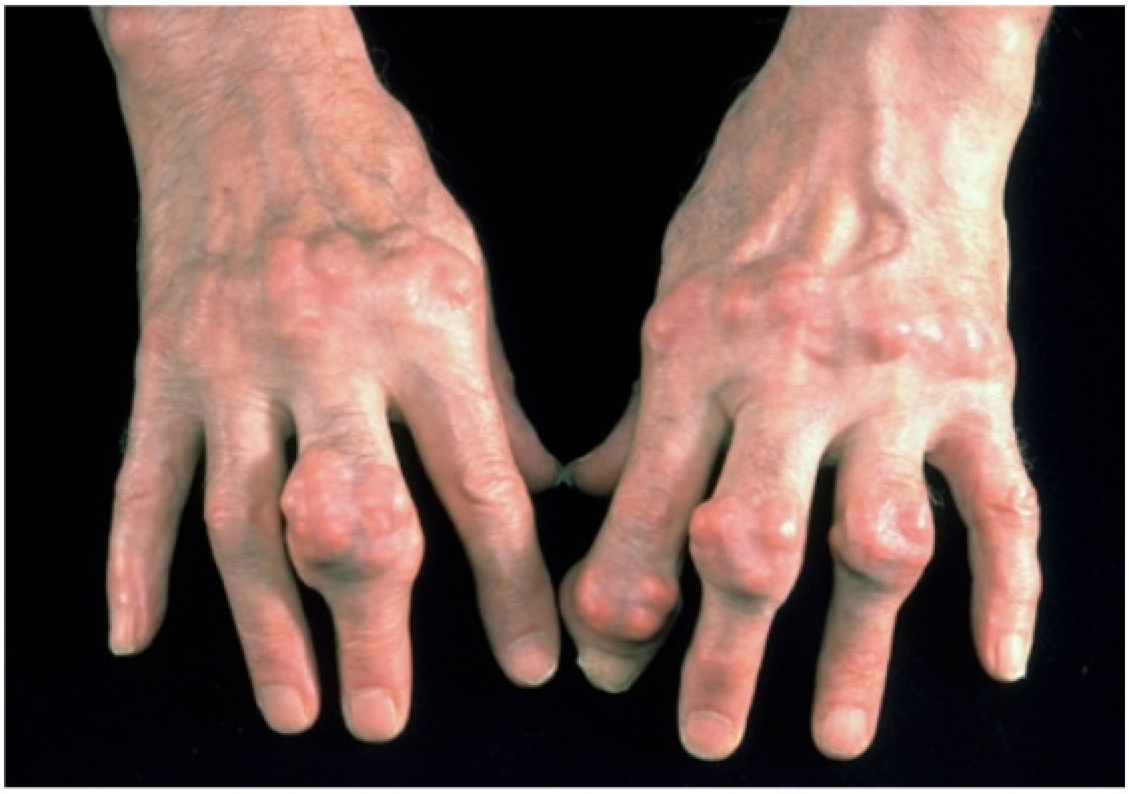
1.4.9 Rituximab (Rituxan, Anti-CD20)

Rituximab is a chimeric *monoclonal antibody against CD20* approved for treatment of severe rheumatoid arthritis. It is also used as chemotherapy for *B lymphocyte related leukemias* and lymphomas.

As a foreign protein, rituximab can cause infusion reactions. It can also cause complications due to immune suppression, including *reactivation of hepatitis B* and other viruses. A rare adverse effect is *progressive multifocal leukoencephalopathy (PML),* an often fatal disease caused by *activation of JC virus*.

2 Therapies for Gout

Gout is a disorder resulting from crystallization of uric acid in joints with a subsequent inflammatory reaction by neutrophils. Gout therapies either relieve acute symptoms or reduce risk of gouty attacks by lowering uric acid pool. Uric acid is an end product of purine metabolism.



Medican/Visuals Unlimited, Inc.

▲**Figure 11–2.0** Gouty Joints

2.1 Therapeutic Approach to Gout

The therapeutic approach to gout is first to lessen the often excruciatingly painful acute symptoms and then to reduce risk of recurrence. Different drugs are used for these two therapeutic goals.

2.2 Therapies for Acute Gout Attacks

Gout attacks can be very painful, so fast pain relief is a high priority.

2.2.1 NSAIDs (Indomethacin)

NSAIDs, particularly *indomethacin,* are first-line therapy for acute gout attacks. These drugs act by reducing the inflammation associated with gout.

2.2.2 Colchicine

Colchicine *inhibits neutrophil mobility and activity,* thereby quickly reducing the joint inflammation associated with gout attacks.

Colchicine's major limitation is its toxicity. Although highly effective in relieving acute gout attacks, the drug has *narrow therapeutic index*. The most common adverse effects are gastrointestinal upset and *neutropenia*. Overdose of colchicine can be life-threatening.

2.2.3 Intra-Articular Injection of Corticosteroids

Glucocorticoids are nearly as effective as NSAIDs in relieving *acute gouty attacks*. Steroids can be injected directly into the affected joint.

2.3 Therapies for Chronic Management of Gout and Other Hyperuricemic Conditions

There are multiple approaches to the chronic management of gout. Some therapies and diet modification reduce serum uric acid levels. The uricosuric drugs increase uric excretion.

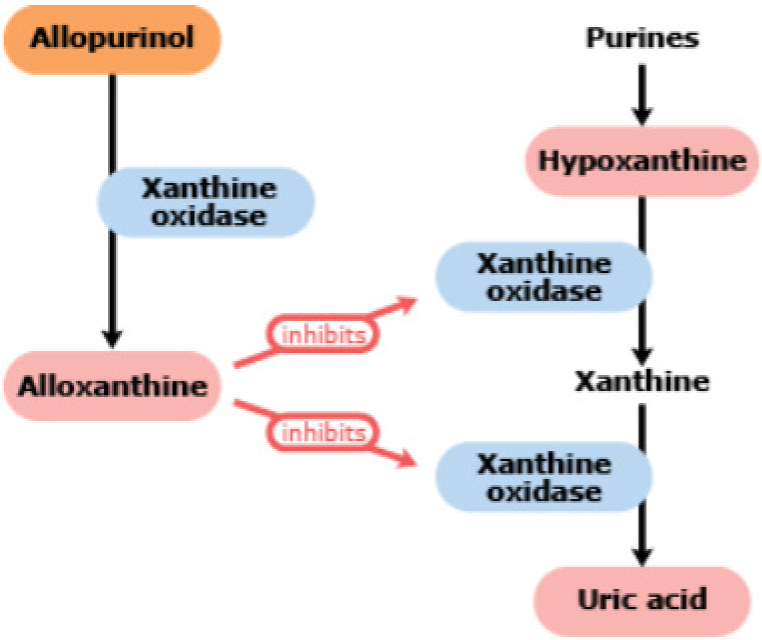
2.3.1 Dietary Modifications

Certain foods and drinks can worsen or reduce hyperuricemia and thereby affect probability of symptomatic gout.

- **Gout-Promoting Foods and Drinks:** Red meats, beer (and, to a lesser degree, other alcoholic beverages), seafood, and fructose-containing beverages increase uric acid levels and chances of gout attacks.
- **Gout-Reducing Foods and Drinks:** Cherries, whole grains (with complex carbohydrates), and coffee have been shown to reduce risk of gout attacks.

2.3.2 Allopurinol

Allopurinol *inhibits xanthine oxidase,* the enzyme that catalyzes the last step in the conversion of purines to uric acid (xanthine → uric acid). Allopurinol is used both in *chronic gout* and in managing hyperuricemia associated with *tumor lysis syndrome*. The latter use is being steadily replaced by rasburicase (see below), a recombinant uricase that can reduce high uric acid levels more rapidly than allopurinol.



▲**Figure 11–2.3** Action of Allopurinol on Uric Acid Pathway

Important Concept

Be careful not to confuse therapies for acute and chronic gout. For example, colchicine is not an appropriate therapy for management of chronic gout. Likewise, allopurinol is an ineffective treatment for an acute gout attack.

Allopurinol has two major drawbacks: complex dosing and high frequency of dermatologic reactions, including *Stevens-Johnson syndrome* and *toxic epidermal necrolysis*. Severe dermatologic reactions are associated with the HLA-B*5801 allele (genetic testing to detect this is available). Allopurinol also increases risk of *bone marrow toxicity* when used in patients who have received 6-mercaptopurine or its prodrug azathioprine. This is because xanthine oxidase is one of the enzymes involved in the clearance of 6-mercaptopurine.

2.3.3 Uricosuric Drugs

Uricosuric drugs increase rate of *excretion of uric acid* and thereby reduce risk of gout attacks. *Probenecid* and *sulfinpyrazone* are the most common uricosuric drugs. These drugs are generally well tolerated, but act slowly and are not always effective.

2.3.4 Uricases

Uricases are enzymes that *break down uric acid into allantoin*, a compound that is much more water-soluble than uric acid. Uricases were originally used therapeutically to reduce uric acid in the tumor lysis syndrome. Hyperuricemia can occur in leukemias and lymphomas with very high levels of circulating tumor cells. These cells are highly active in DNA synthesis and produce abundant uric acid from purine turnover. Uricase is now being used to *treat gout refractory to other therapies*.

- **Rasburicase:** This recombinant uricase is approved for the treatment and prevention of hyperuricemia associated with tumor lysis syndrome. It is highly effective in dramatically lowering serum uric acid levels and preventing crystallization of uric acid in the kidneys. Rasburicase cannot typically be used long-term due to immunogenicity and very high cost.
- **Pegloticase:** This polyethylene glycol (PEG)–modified uricase has longer elimination half-life and lower immunogenicity than rasburicase. Pegloticase can be used for *longer-term management of chronic gout* refractory to other therapies. Like rasburicase, high cost is an issue.

3 Drugs Affecting Calcium and Bone Structure

Diseases of the bone are very common, with osteoporosis being a leading underlying cause of fractures.

3.1 Calcium Supplementation

Adequate dietary calcium in childhood and young adult years is important in building bone mineral density. Adults at risk for osteoporosis are encouraged to take calcium supplementation to maintain bone density or at least minimize bone density loss.

3.2 Vitamin D

Vitamin D deficiency is *common in Western countries* due to limited sunlight exposure and low vitamin D intake in diet. Vitamin D deficiency can lead to *hypocalcemia* and *secondary hyperparathyroidism,* which causes calcium loss from bones. Institute of Medicine recommends at least 600 IU of vitamin D per day up to age 70 and at least 800 IU for those older than 70.

3.3 Bisphosphonates

Bisphosphonates stabilize hydroxyapatite bone structure by *inhibiting function of osteoclasts* (cells that promote bone resorption).

Therapeutic Uses Bisphosphonates are used in a variety of conditions associated with fragile bone (hypercalcemia of malignancy, osteoporosis, osteogenesis imperfecta) or excessive bone turnover (Paget disease). The most common first-line bisphosphonates are *alendronate* and *risedronate*. Intravenous pamidronate is used if these front-line drugs cannot be used or are ineffective.

Adverse Effects Oral bisphosphonates are associated with inflammation and erosions of the stomach and esophagus. Bisphosphonates, especially the intravenous formulations, have been associated with *osteonecrosis,* particularly of the mandible and maxilla, and unusual fractures.

3.4 Calcitonin

Calcitonin is a hypocalcemic peptide hormone produced by parafollicular C cells of the thyroid gland. Calcitonin *inhibits osteoclastic bone resorption*. Either salmon calcitonin or recombinant human calcitonin is available. Calcitonin is administered as intranasal spray; oral formulations are ineffective due to proteolytic digestion.

Therapeutic Uses Calcitonin is used for treatment of *postmenopausal osteoporosis* and to rapidly lower serum calcium in hypercalcemic states such as *hypercalcemia of malignancy* (e.g., due to paraneoplastic syndrome associated with squamous cell carcinomas).

Adverse Effects Calcitonin intra-nasal spray is generally well-tolerated. The most common adverse effects are related to irritation of the nose and sinuses.

CHAPTER 12 Toxicology

1 Overview of Drug Adverse Effects

Toxicology is the study of the adverse effects of drugs, which include any effect that varies from a drug's intended therapeutic effect, harmful or otherwise.

1.1 Extensions of Expected Actions of Drugs

Some adverse effects are extensions of the expected physiologic effects of the drug and are dose-dependent, getting stronger as dose increases. One example is respiratory depression by high doses of barbiturates, benzodiazepines, ethanol, or other sedative-hypnotics. Another example is bradycardia and AV block by β-blockers.

1.2 Idiosyncratic (Unknown Cause) Adverse Effects

Some adverse effects occur unpredictably and are dose-independent, such that even small doses of drug can cause problems. Many of these types of adverse effects are immune-mediated. A classic example is aplastic anemia caused by chloramphenicol, a rare (1 in ~25,000–30,000) but life-threatening adverse effect.

1.3 Genetically Determined Drug Toxicity

There are a number of examples of genetic differences that lead to drug toxicity.

1.3.1 Plasma Cholinesterase Deficiency

Plasma cholinesterase (also known as pseudocholinesterase or butyrylcholinesterase) is an enzyme that has unclear physiologic function but is important in metabolizing two normally short-acting neuromuscular blocking agents: succinylcholine and mivacurium. Individuals with plasma cholinesterase deficiency experience prolonged muscle paralysis following administration of succinylcholine and mivacurium. When this occurs, patients need to be ventilated until the drugs slowly clear by alternative metabolic routes.

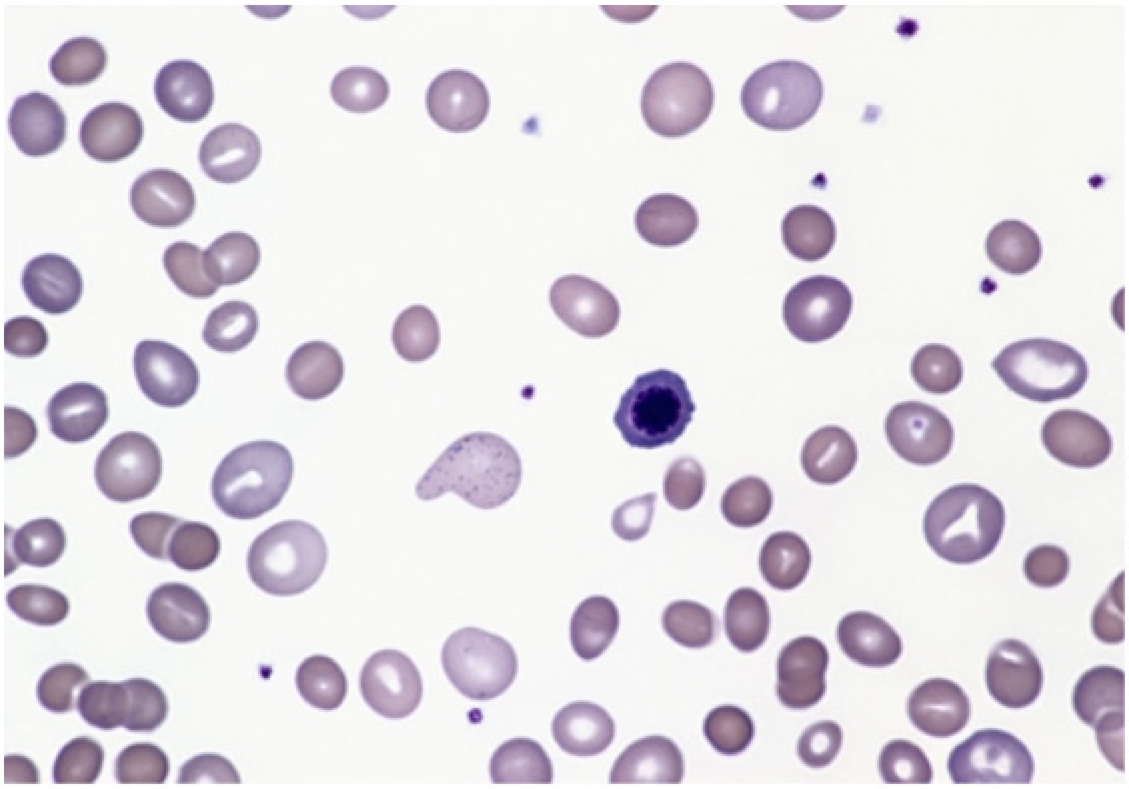
USMLE® Key Concepts

For Step 1, you must be able to:

- Describe common adverse effects seen with medication therapy.
- List the antidotes associated with common drug overdoses.
- Explain the adverse effects that drugs may cause to the developing fetus and breast-feeding infant.
- Define the FDA classification for safety of drugs used in pregnancy.

1.3.2 Glucose-6-phosphate Dehydrogenase (G6PD) Deficiency

G6PD deficiency is classically associated with hemolytic anemia following the use of oxidant drugs (chloroquine, primaquine, dapsone, nitrofurantoin) or ingestion of certain foods such as fava beans. A characteristic finding is the presence of bite cells and blister cells in the peripheral blood smear. These cells result from attempts by the spleen to remove damaged red blood cells from the circulation. Heinz bodies resulting from denatured hemoglobin may also be seen.



Dr. Gladden Willis/Visuals Unlimited, Inc.

▲**Figure 12-1.3** Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

1.3.3 Porphyrias

The porphyrias are a complex group of disorders involving defects in the synthetic pathway for heme. Two of the porphyrias (acute intermittent porphyria, variegate porphyria) are characterized by acute attacks presenting with abdominal pain and/or neurologic symptoms. Phenobarbital and other liver enzyme *"inducers"* can precipitate porphyria attacks by stimulating the heme synthesis pathway. In patients with genetic defects in the pathway, stimulation of heme synthesis leads to accumulation of toxic intermediates and clinical symptoms.

2 Signs and Symptoms of Toxicity

In approaching Step 1 questions related to drug toxicity, it is essential to know the signs and symptoms of toxicity and the agents most likely to cause them. Common signs and symptoms of toxicity include comatose state, constricted pupils (miosis), dilated pupils (mydriasis), cardiac arrhythmias, hyperthermia, metabolic acidosis/anion gap, elevated osmolal gap, and hepatic failure.

2.1 Comatose State

A variety of drugs can cause a patient to present in a comatose state. In general, think of central nervous system (CNS) depressants such as ethanol, barbiturates, benzodiazepines, and opiates. Sometimes people fail to consider ethylene glycol (antifreeze) and methanol (windshield fluid) as CNS depressants, but these compounds can cause a comatose state in addition to their more specific organ toxicities (renal damage for ethylene glycol, blindness for methanol). For clinical scenarios involving suspected "date rape," GHB (gamma-hydroxybutyrate) and flunitrazepam (Rohypnol) are drugs that dissolve in drinks easily and can rapidly bring on a comatose state. The CNS depressant effects of ethanol can be related to blood alcohol concentration (BAC).

▼**Table 12-2.1** Blood Alcohol Concentration

BAC (mg/dL)	Clinical Effect
50–100	Sedation, mild euphoria, disinhibition, impaired reasoning, slower reaction times
100–200	Motor impairment, slurred speech, ataxia
200–300	Emesis, stupor, acute CNS depression, blackout
300–400	Bradyardia, comatose state
>400	Respiratory depression, death

Katsung, Bertram et al, *Basic and Clinical Pharmacology*, 12th ed. © 2012 The McGraw-Hill Companies, Inc.

2.2 Constricted Pupils (Miosis)

The most common drugs to cause miosis are the opioids, which in overdose classically cause pinpoint pupils, respiratory depression, and a comatose state. An exception is meperidine, which has some antimuscarinic effects. In term of toxic exposures, organophosphate insecticides will cause miosis from the stimulation of the parasympathetic system by inhibition of acetylcholinesterase.

2.3 Dilated Pupils (Mydriasis)

Drugs can dilate pupils by adrenergic (sympathetic) stimulation or by blocking muscarinic receptors. Amphetamines (including methamphetamine and MDMA/Ecstasy) and cocaine stimulate the adrenergic system. Phenothiazine antipsychotics (chlorpromazine, thioridazine) and tricyclic antidepressants (especially amitriptyline) inhibit muscarinic receptors and thereby dilate pupils.

2.4 Cardiac Arrhythmias

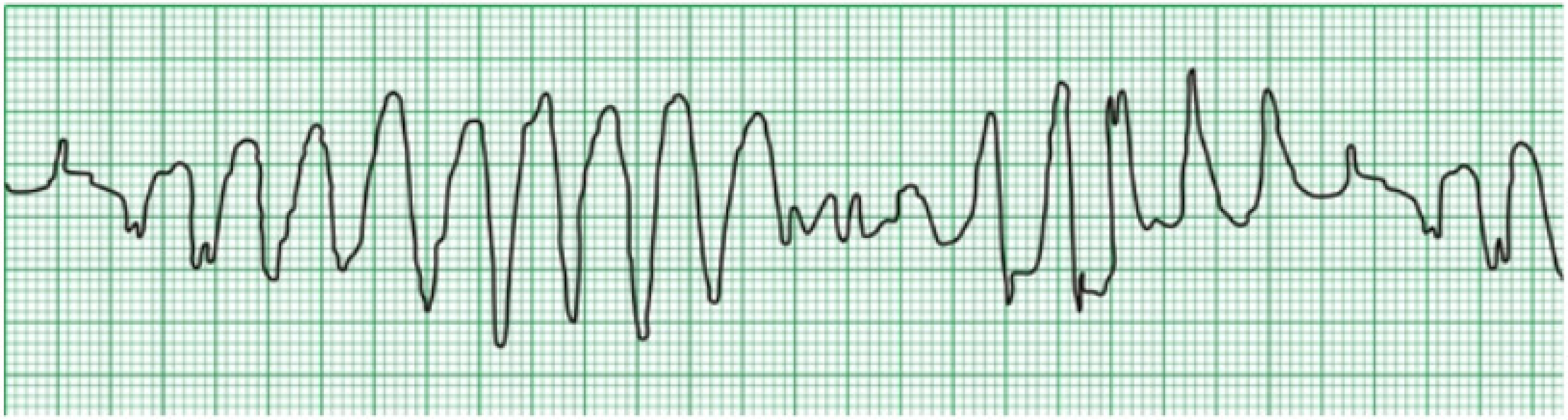
Cardiac arrhythmias can result from over-stimulation of the heart or by more specific effects on ion channels.

2.4.1 Overstimulation of the Heart

Amphetamines and cocaine increase heart rate and excitability by increasing the release of NE from the sympathetic nervous system. Particularly in overdose, this can lead to arrhythmias. Phenothiazine antipsychotics and tricyclic antidepressants increase heart excitability by blockage of muscarinic receptors and voltage-gated sodium channels. Digoxin is also prone to causing arrhythmias.

2.4.2 Long QT Syndrome

A number of drugs prolong the QT interval of the EKG, often by blocking cardiac repolarization, as occurs in the inhibition of potassium channels. The QT interval may also become prolonged by hypokalemia or a hereditary trait known as the Ward-Romano syndrome. A long QT is usually asymptomatic on its own but can progress to torsade de pointes, a form of ventricular tachycardia that can degenerate to fatal ventricular fibrillation. Drugs that classically can cause prolonged QT include cardiac drugs with class III antiarrhythmic properties (quinidine, amiodarone, sotalol) and the phenothiazine antipsychotics. A very popular antihistamine drug, terfenadine (Seldane), was removed from the U.S. market in 1998 due to fatal arrthythmias related to QT prolongation.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▲ **Figure 12-2.4** Long QT Progressing to Torsade de Pointes

2.5 Hyperthermia

Hyperthermia can arise from a number of drugs. Serotonin syndrome, neuroleptic malignant syndrome, and malignant hyperthermia are discussed in neuropharmacology (chapter 4). In terms of drugs of abuse, Ecstasy (MDMA, a methamphetamine derivative) classically causes over-heating. Patients may complain of extreme thirst or even use ice on their bodies to try to cool down. Antimuscarinics including atropine and tricyclic antidepressants can also increase body temperature.

2.6 Anion Gap Metabolic Acidosis

There are a number of drugs and conditions that can result in an anion gap metabolic acidosis.

Causative agents include methanol (found in windshield fluid and some cleaning agents), paraldehyde (no longer used clinically), propylene glycol, ethylene glycol, isoniazid, iron, and salicylates. Causative conditions include uremia (from renal failure), diabetic ketoacidosis (often together with very high plasma glucose), and lactic acidosis.

A metabolic acidosis can be detected by arterial blood gas analysis or by a decreased bicarbonate on electrolyte panels. Anion gap is calculated as $[\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_{3-}])$. Anion gaps greater than 16 are considered abnormal.

Memory Aid

"Mudpiles" cause anion gap metabolic acidosis:

M – **M**ethanol
U – **U**remia
D – **D**iabetic ketoacidosis
P – **P**araldehyde
or **P**ropylene glycol
I – **I**soniazid or iron
L – **L**actic Acidosis
E – **E**thylene glycol
S – **S**alicylates

2.7 Osmol Gap

The most common substances that can cause an elevated osmol gap are ethanol, ethylene glycol, isopropanol, methanol, and propylene glycol. Propylene glycol is a diluent in some intravenous medications such as lorazepam and phenytoin. Other possible causes of an elevated osmol gap are kidney failure, diabetic ketoacidosis, and mannitol infusion.

▼**Table 12-2.7** Agents Causing Osmol Gap

Substance	Serum Level (mg/dL)	Corresponding Osmol Gap (mOsm/kg)
Ethanol	350	75
Methanol	80	25
Ethylene glycol	200	35
Isopropanol	350	60

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2.8 Hepatic Failure

The leading cause of drug-induced *acute liver failure* is acetaminophen, and this is discussed in more detail below. MDMA/Ecstasy is a rare cause of acute liver failure. The most common drug causing *chronic liver failure* is ethanol. Statins, niacin, methotrexate, and amiodarone can cause chronic liver damage, as shown by elevated liver enzymes, although these drugs very rarely cause liver failure.

▼**Table 12-2.8** Overdose and Withdrawal

Drug	Overdose Effects	Withdrawal Symptom
Amphetamines, cocaine, methylphenidate	Hypertension, tachycardia, delusions, hallucinations, hyperthermia, seizures, death	Apathy, irritability, increased sleep time, disorientation, depression
Ethanol, barbiturates, benzodiazepines	Slurred speech, motor impairment, dilated pupils, weak and rapid pulse, clammy skin, depressed CNS, respiratory depression, coma, death	Anxiety, insomnia, delirium, tremors, seizures, death
Opioids	Constricted pupils, clammy skin, nausea, drowsiness, respiratory depression, coma, death	Nausea, chills, cramps, lacrimation, rhinorrhea, yawning, hypernea, tremor

Trevor, Anthony et al, *Katzung & Trevor's Pharmacology Examination and Board Review*, 8th ed. © 2008 The McGraw-Hill Companies, Inc.

3 Common Toxicities and Their Management

For USMLE Step 1, it is important to know the toxicities most frequently encountered in clinical settings and the antidotes and other therapies used to manage them. With many of the agents discussed in this section, the difference between a therapeutic effect and a toxic effect is a matter of dose. Other agents such as cyanide and organophosphates are toxic to humans no matter what the dose.

▼**Table 12-3.0** Common Antidotes

Antidote	Poison(s)
Acetylcysteine (Acetadote, Mucomyst)	Acetaminophen
Atropine	Anticholinesterase intoxication; organophosphates, carbamates
Bicarbonate, sodium	Membrane-depressant cardiotoxic drugs (tricyclic antidepressants, quinidine, etc.)
Calcium	Fluoride; calcium channel blockers
Deferoxamine	Iron salts
Digoxin antibodies	Digoxin and related cardiac glycosides
Esmolol	Theophylline, caffeine, metaproterenol
Ethanol	Methanol, ethylene glycol
Flumazenil	Benzodiazepines
Fomepizole	Methanol, ethylene glycol
Glucagon	β-blockers
Hydroxocobalamin	Cyanide
Naloxone	Narcotic drugs, other opioid derivatives
Oxygen	Carbon monoxide
Physostigmine	Suggested for delirium caused by anticholinergic agents
Pralidoxime (2-PAM)	Organophosphate (OP) cholinesterase inhibitors

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3.1 Anticoagulants

Heparin and warfarin are the most commonly prescribed anticoagulants, although newer drugs have been steadily gaining in popularity.

3.1.1 Heparin

Heparin enhances the activity of antithrombin III, which in turn inhibits the clotting cascade. The antidote for heparin overdose is protamine sulfate, a chemical antagonist that binds to and inactivates heparin. Protamine sulfate is used in many cardiac procedures (e.g., cardiopulmonary bypass) to reverse heparin anticoagulation once the procedure is over.

3.1.2 Warfarin

Warfarin inhibits the vitamin K-dependent synthesis of the clotting factors II, VII, IX, and X and additionally the "natural" anticoagulants protein C and protein S. *Warfarin is one of the classic low-therapeutic-index drugs*, and patients may end up with excessive anticoagulation and bleeding risk as measured by an elevated prothrombin time/international normalized ratio (PT/INR). In addition to warfarin, many rat poisons, such as brodifacoum, contain long half-life coumarins. The two main therapies for excessive warfarin are vitamin K_1 and infusion of *fresh frozen plasma*. Vitamin K_1 is preferred if the risk of bleeding is low. More urgent situations require fresh frozen plasma, which contains clotting factors (from the donor), but also carries risks associated with blood product transfusions. Ingestion of rat poisons may require months of vitamin K_1 supplements.

3.2 Carbon Monoxide

Carbon monoxide (CO) poisoning may be encountered in accidental settings, as in a poorly ventilated room with a heater, or in suicide attempts. *Carbon monoxide poisons hemoglobin* and impairs oxygen delivery. The management of carbon monoxide is to remove the patient from exposure and administer oxygen. In severe overdoses, high-pressure (hyperbaric) oxygen may be necessary.

3.3 Central Nervous System (CNS) Depressants

The CNS depressants include barbiturates, benzodiazepines, ethanol, ethylene glycol, isopropanol, methanol, and opiates. Some of these compounds have antidotes, while others do not.

3.3.1 Barbiturates

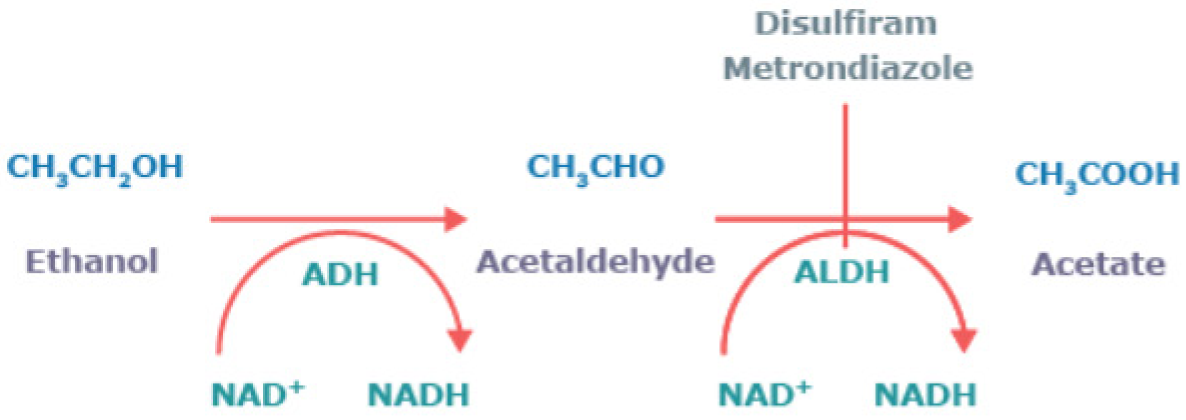
There is *no specific antidote for barbiturates*. These drugs are quite dangerous in overdose, but fortunately have been mainly replaced as sleeping pills and anxiolytics by safer drugs such as benzodiazepines, eszopiclone, and zolpidem.

3.3.2 Benzodiazepines

The benzodiazepines are a large class of drugs that include alprazolam, clonazepam, chlordiazepoxide, diazepam, flunitrazepam, lorazepam, and temazepam. Although the benzodiazepines are much safer in overdose than barbiturates, large ingestions, especially together with other CNS depressants, can be life-threatening. Benzodiazepines have a specific antidote, flumazenil, that blocks the benzodiazepine binding site on the $GABA_A$ receptor.

3.3.3 Ethanol

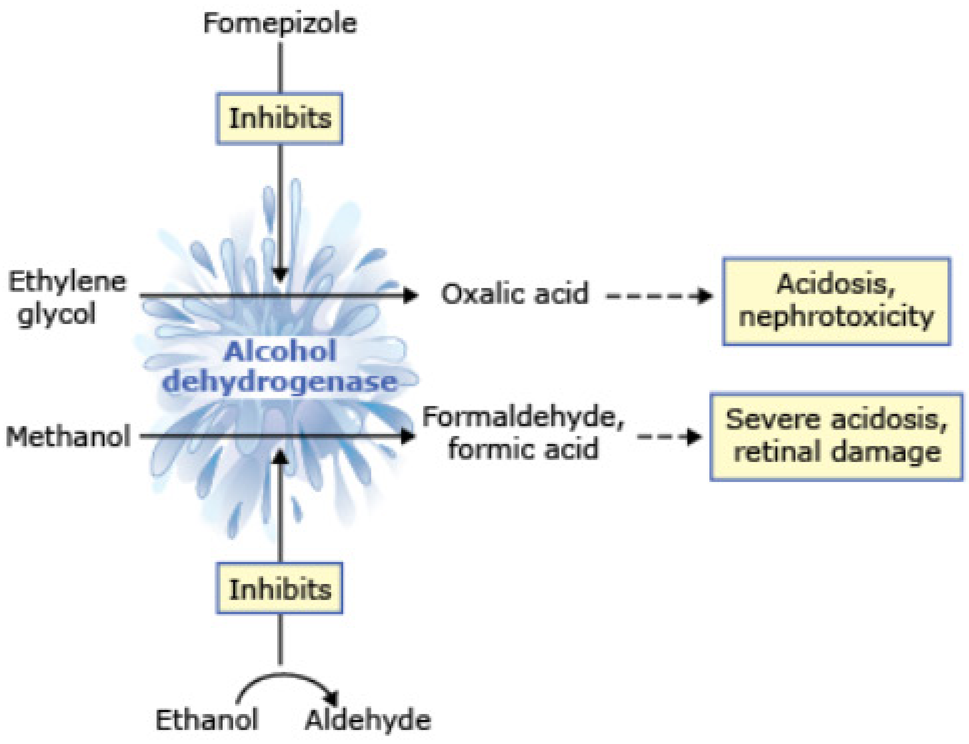
Ethanol is metabolized first by alcohol dehydrogenase (rate-limiting step) and then by aldehyde dehydrogenase. Some individuals, especially from East Asia, have limited aldehyde dehydrogenase activity and experience unpleasant symptoms, such as flushing and nausea, with small amounts of ethanol. Disulfiram, cefotetan, griseofulvin, and metronidazole can also produce a similar reaction by inhibiting aldehyde dehydrogenase, producing a "disulfiram-like" effect (nauea and vomiting). There is no specific antidote for ethanol. Treatment is supportive.


Disulfiram
Metrondiazole
CH_3CH_2OH
Ethanol
ADH
NAD+
NADH
CH_3CHO
Acetaldehyde
ALDH
NAD+
NADH
CH_3COOH
Acetate

▲ **Figure 12-3.3A** Ethanol Metabolism

3.3.4 Ethylene Glycol and Methanol

Ethylene glycol is found in automobile antifreeze, while methanol is found in windshield fluid and cleaning solvents. Both compounds cause damage through toxic metabolites. Ethylene glycol is metabolized to *oxalate*, which crystallizes in the kidney. Methanol is metabolized to *formic acid*, which can destroy the optic nerve and cause blindness. The treatment for ethylene glycol and methanol ingestion is either ethanol or fomepizole (4-methylpyrazole). Ethanol saturates the alcohol dehydrogenase enzyme and prevents formation of toxic metabolites. Fomepizole directly inhibits alcohol dehydrogenase and is generally safer to administer than intravenous ethanol but does have downside of high costs (~$1,200/dose). Severe overdoses are treated with renal dialysis.


Fomepizole
Inhibits
Ethylene glycol
Oxalic acid
Acidosis, nephrotoxicity
Alcohol dehydrogenase
Methanol
Formaldehyde, formic acid
Severe acidosis, retinal damage
Inhibits
Ethanol
Aldehyde

▲ **Figure 12-3.3B** Metabolism of Ethylene Glycol and Methanol

3.3.5 Isopropanol

Isopropanol is found in rubbing alcohol and is generally much less toxic than ethylene glycol or methanol because it is metabolized to relatively non-toxic acetone. As with ethanol, there is no antidote, and ingestions are managed by supportive care.

3.3.6 Opiates

Opiate overdose can present with *respiratory depression* and a comatose state. The specific antidote for opiates (codeine, morphine, hydrocodone, oxycodone, etc.) is *naloxone*, an antagonist of the μ-opioid receptors. Naloxone is often given empirically in emergency settings if opiate overdose is suspected. A longer-acting opiate antagonist is naltrexone, which is used for treatment of opiate addiction.

3.4 Cyanide

Cyanide is a rapidly acting poison of the electron transport chain essential for cellular respiration. Patients may present with cyanosis and a reduced arterial-venous oxygen saturation difference because of the inability of tissues to use oxygen. The traditional antidote for cyanide poisoning is amyl nitrite or sodium nitrite (not to be confused with nitrates). This forms methemoglobin, which then combines with cyanide. Recently, there has been a shift towards *hydroxocobalamin*, a vitamin B_{12} derivative. An alternative antidote is *sodium thiosulfate*, which combines with cyanide to form the less toxic thiocyanate.

3.5 Digoxin

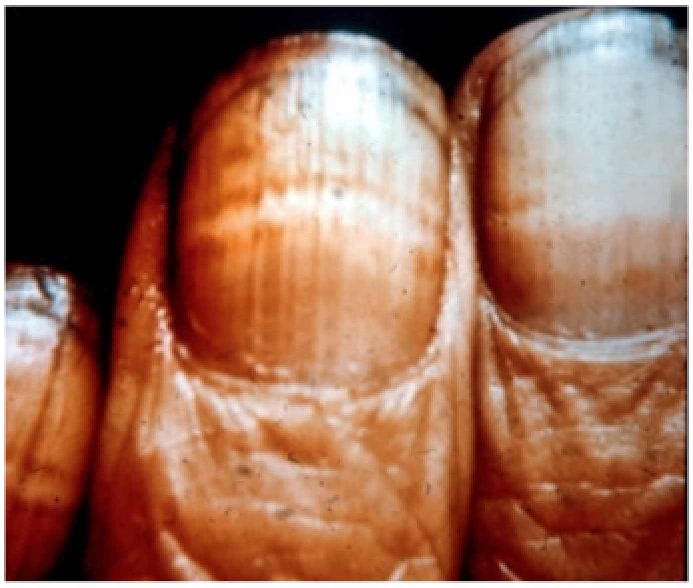
Digoxin is a cardiac glycoside that inhibits the Na^+/K^+ ATPase. Digoxin toxicity manifests as nausea, vomiting, visual change (green and yellow auras), mental status changes, and cardiac arrhythmias. The specific antidote for digoxin is a digoxin-specific Fab fragment generated from mouse monoclonal antibodies. The main downside is the high cost of the antidote (> $5,000/dose).

3.6 Heavy Metals

The heavy metals include lead, mercury, and arsenic. In poisonings of these metals, the first priority is to remove the exposure. In more severe cases, chelation therapy may be used.

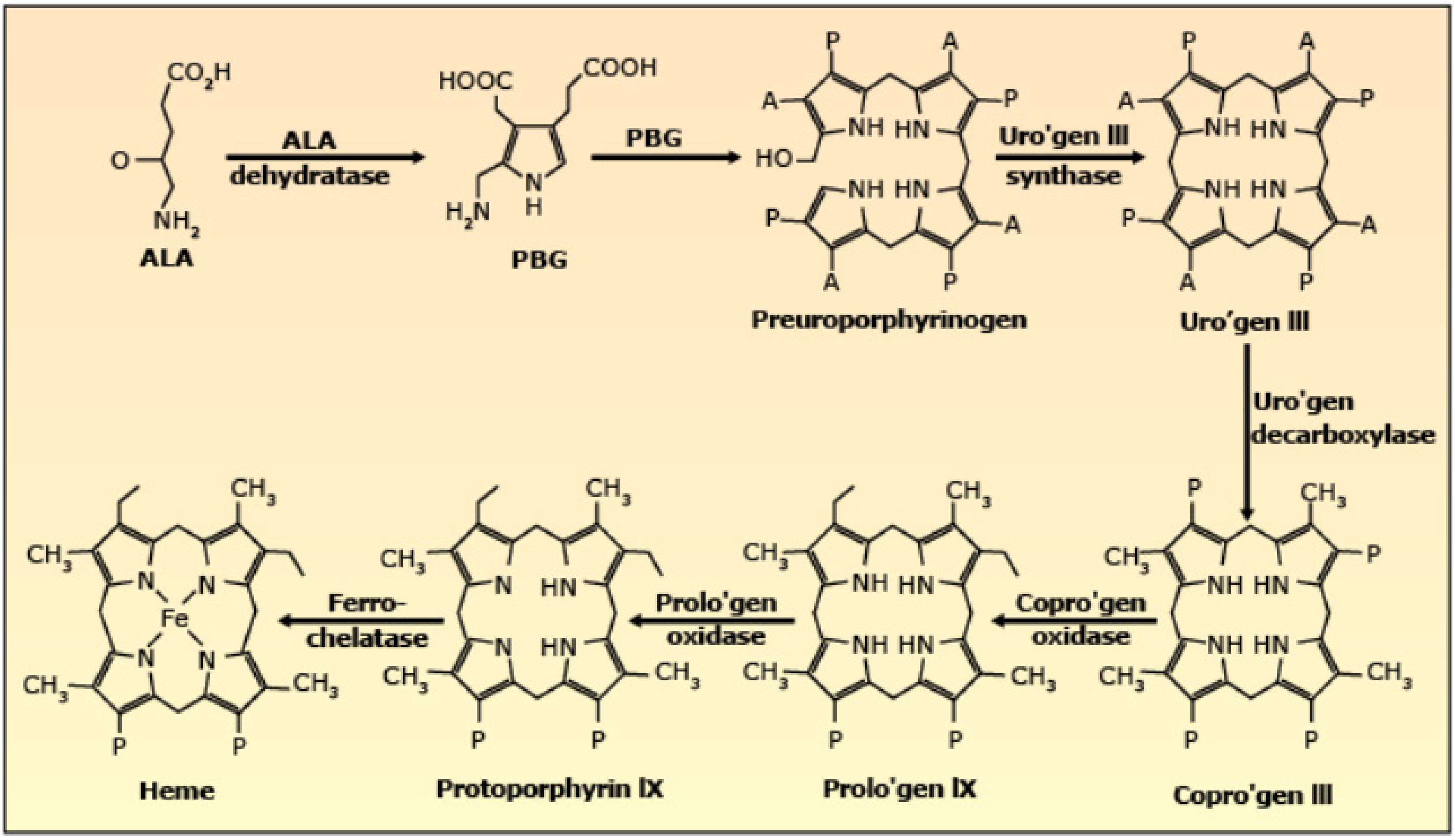
3.6.1 Lead

Sources of lead include lead paint (generally in older homes built before the 1970s), retained bullets, and leaded glaze on ceramics. Lead inhibits heme synthesis (inhibition of δ-aminolevulinate dehydratase and ferrochelatase) and can cause basophilic stippling of erythrocytes. Chronic symptoms include *neuropathy* (wrist drop), gastrointestinal pain, *leukonychia* (discoloring of nails), and lead lines in the bones, especially the distal radius. Abdominal colic may be the only symptom in young children. Acute ingestions of paint chips can be seen on abdominal X-ray. The first step is to remove the patient from the source of exposure. Chelation therapy is used in severe cases and includes, in order of preference: *succimer (DMSA; 2,3-dimercaptosuccinic acid), EDTA, penicillamine,* and *dimercaprol*. Succimer is the only one of these agents that can be given orally. In the hospital setting, EDTA is the intravenous agent of choice.

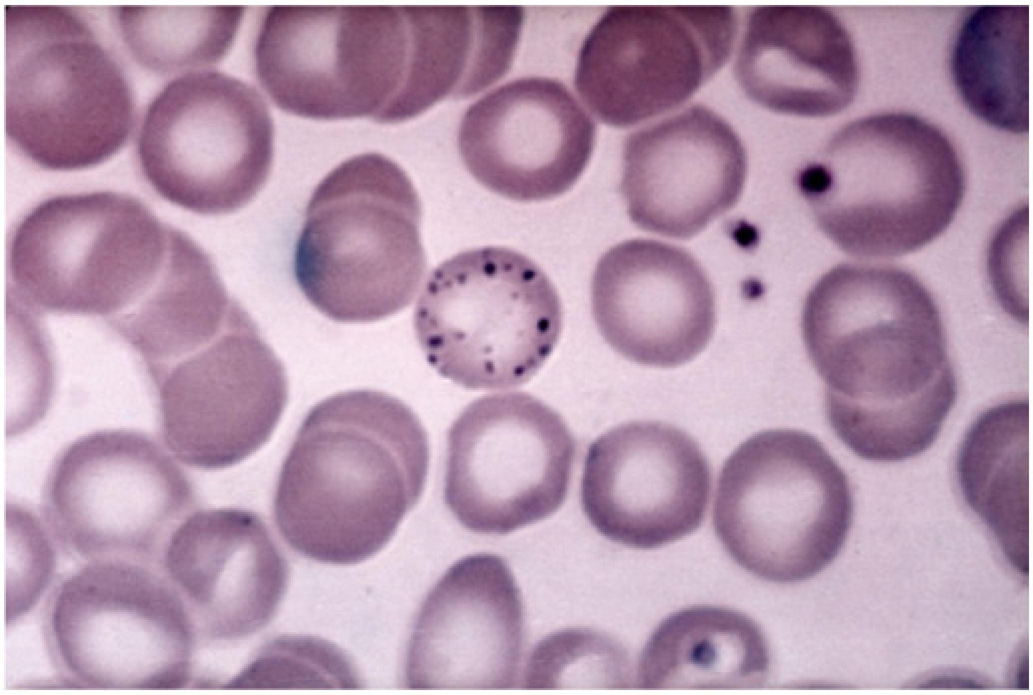


OJ Staats MD/Custom Medical Stock Photo

▲ **Figure 12-3.6A** Leukonychia Caused by Lead Poisoning


ALA
ALA dehydratase
PBG
PBG
Preuroporphyrinogen
Uro'gen III synthase
Uro'gen III
Uro'gen decarboxylase
Copro'gen III
Copro'gen oxidase
Prolo'gen IX
Prolo'gen oxidase
Protoporphyrin IX
Ferro-chelatase
Heme

▲**Figure 12-3.6B** Inhibition of Heme Synthesis by Lead



Wellcome Images

▲**Figure 12-3.6C** Basophilic Stippling

3.6.2 Mercury

The most common source of mercury in the United States is fish, especially top predators such as marlin, tilefish, orange roughy, shark, swordfish, tuna, and king mackerel. Organic mercury (methylmercury) is much more toxic than inorganic mercury. Mercury exposure can cause a variety of health problems include pulmonary fibrosis, neurologic impairment ("Mad Hatter disease"), and birth defects. If chelation therapy is necessary, *dimercaprol* is the agent of choice.

3.6.3 Arsenic

The most common source of arsenic poisoning is contaminated ground water. Symptoms of chronic arsenic poisoning are headaches, confusion, diarrhea, and changes in fingernail pigmentation (leukonychia). More severe intoxications lead to convulsions, abdominal pain, and coma. *Dimercaprol* is the chelator of choice.

3.7 Iron Poisoning

Iron poisoning is relatively common, especially in children. The classic symptoms are hemorrhagic gastritis with vomiting and diarrhea. Sometimes iron tablets or pills may be seen on abdominal X-ray. In severe cases, the chelator of choice is *deferoxamine*. Another iron chelator is deferiprone, used mainly for treatment of chronic iron overload (as in a patient with thalassemia who received frequent blood transfusions).

3.8 Isoniazid (INH)

Isoniazid is an anti-tubercular medication that can cause hepatotoxicity and peripheral neuropathy. Liver enzymes are frequently monitored in patients on chronic therapy. The risk of peripheral neuropathy is reduced by pyridoxine (vitamin B_6).

3.9 Organophosphates

Organophosphates are used as insecticides and nerve gases. By blocking acetylcholinesterase, organophosphates increase acetylcholine concentrations, leading to overload of muscarinic and nicotinic acetylcholine receptors. Organophosphate inhibition with acetylcholinesterase are initially reversible, but over the course of hours become irreversible. The classic symptoms of poisoning are miosis, vomiting, diarrhea, bradycardia, skeletal muscle paralysis, and ultimately respiratory failure.

The treatment of poisoning is supportive care (especially respiratory support), *atropine* (to block muscarinic receptor effects), and *pralidoxime*/2-PAM. Pralidoxime prevents organophosphates from irreversibly inhibiting acetylcholinesterase but does not alter the muscarinic or nicotinic receptor effects. A common trick question on the boards will ask about the initial pharmacologic therapy for organophosphate poisoning. This should be atropine. In contrast, the correct answer to a question that asks about *preventing* irreversible inhibition of acetylcholinesterase is pralidoxime.

Important Concept

Common cases of organophosphate poisoning include migrant farm workers and children playing near agricultural fields or spray tanks.

4 Drug-Related Cutaneous Reactions and Hypersensitivity Syndromes

Cutaneous reactions and hypersensitivity syndromes are among the most common adverse effects related to drugs. Many of these reactions are readily reversible and pose no safety risk. Others such as Stevens-Johnson syndrome and toxic epidermal necrolysis can be severe and even life-threatening.

4.1 Cutaneous Drug Reactions

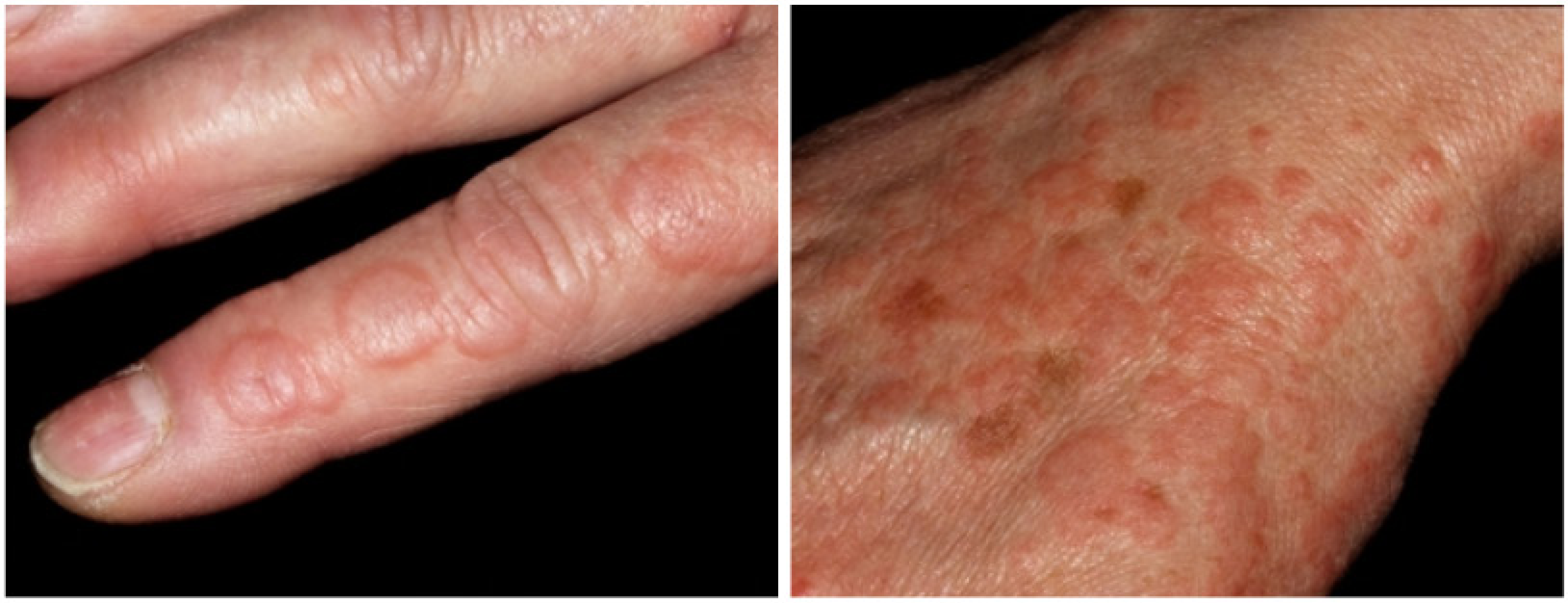
The drugs most frequently implicated in severe cutaneous reactions are anticonvulsants (carbamazepine, phenytoin, phenobarbital, lamotrigine), sulfa antibiotics, penicillins, and cephalosporins. Lamotrigine carries a high rate of dermatologic reactions, so doses are often titrated slowly, discontinuing the drug if any sign of skin reaction appears.

4.1.1 Ampicillin Rash in Mononucleosis Patients

A rash occurs in nearly 100% of those who have infectious mononucleosis and are prescribed ampicilin. This rash does not indicate hypersensitivity to ampicillin or other penicillins and is not a contraindication to using ampicillin in the future.

4.1.2 Erythema Multiforme

Erythema multiforme is a common rash that presents as symmetrical, itchy, erythematous blotches on the extremities. A characteristic sign is "target lesions." There are many causes of erythema multiforme in addition to drugs such as penicillin and sulphonamides, with the most common being herpes simplex and mycoplasma infections. Erythema multiforme is usually benign.

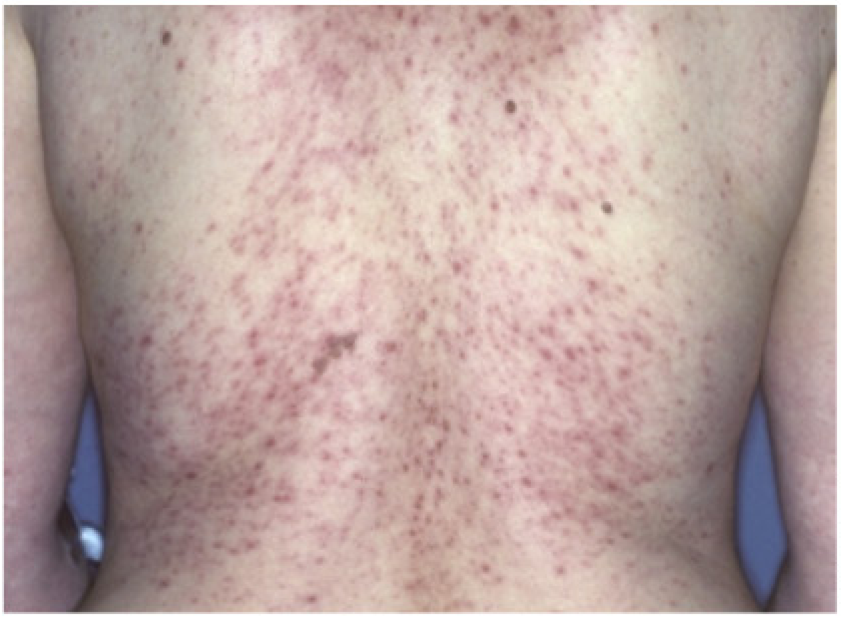


Dr. Nigel Stollery/Photoake, Inc.

▲**Figure 12-4.1A** Target Lesions in Erythema Multiforme

4.1.3 Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) are potentially severe cutaneous reactions that appear to be related. They present with maculopapular rashes and may start with a viral illness-like prodrome, facial and tongue swelling, hives, and skin pain. In Stevens-Johnson syndrome, typically less than 30 percent of the skin is involved. In TEN, skin blisters develop, and whole areas of skin can slough off due to immune damage at the dermal-epidermal layer. Mucous membranes, the esophagus, and the vaginal tract may even become involved. Management of Stevens-Johnson syndrome and TEN involves stopping the offending drug and aggressive supportive care, even admission to a burn unit to protect skin and avoid opportunistic infections. In some patients, immune therapy such as intravenous globulin may be necessary.



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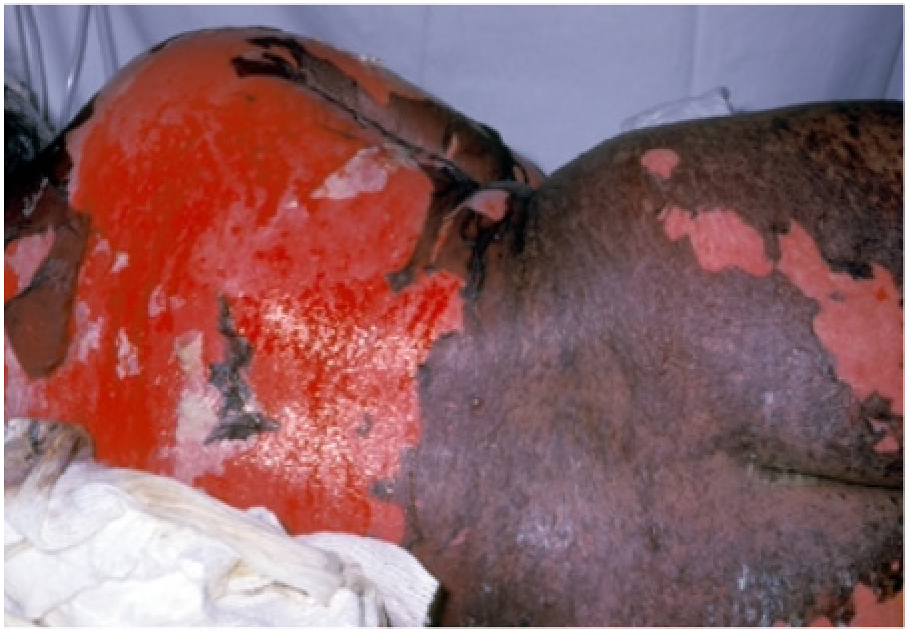
▲**Figure 12-4.1B** Maculopapular Rash in Stevens-Johnson Syndrome



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▲**Figure 12-4.1C** Toxic Epidermal Necrolysis

Skin blistering and sloughing seen in toxic epidermal necrolysis. In this syndrome, the epidermal layer of skin slides off the underlying dermal layer.

4.2 Drug-Related Hypersensitivity Reactions

Drugs are possible causes of all four types of hypersensitivity reactions.

4.2.1 Type I Hypersensitivity Reactions

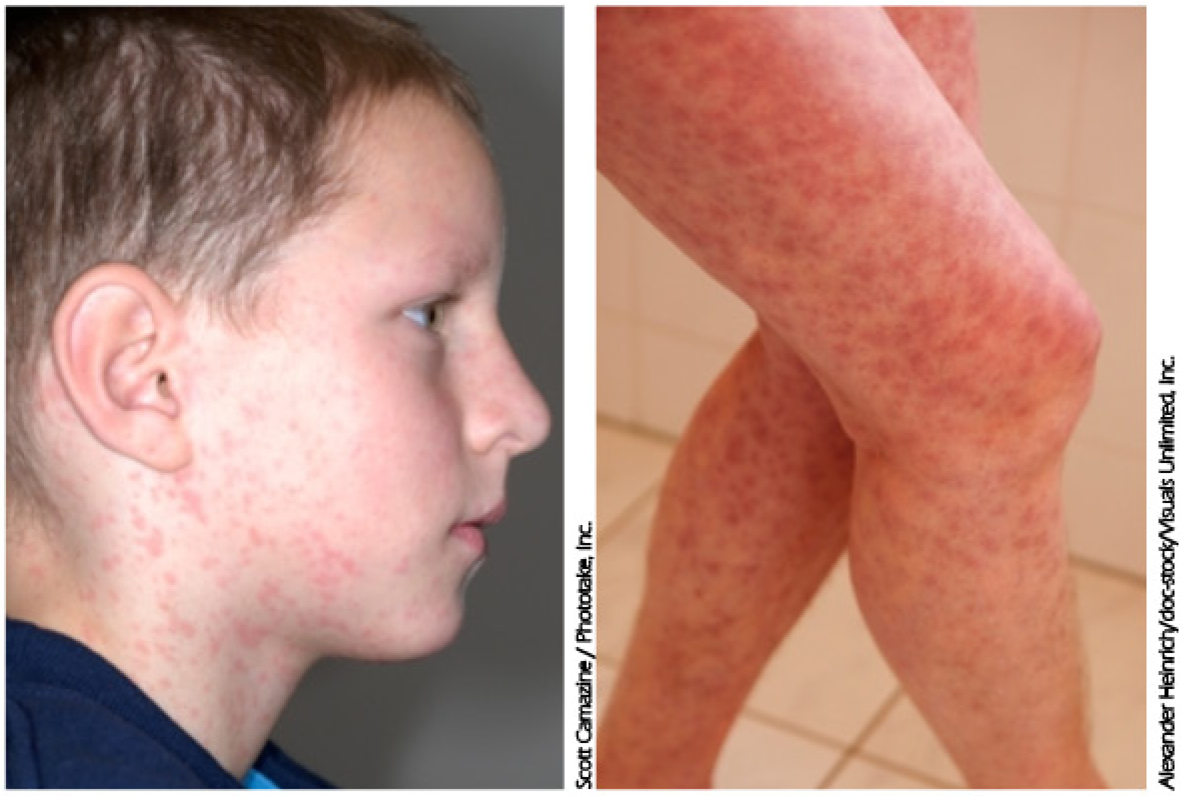
Type I reactions are "anaphylactic" in nature and involve *IgE-mediated* release of inflammatory mediators such as histamine and leukotrienes. Drug causes include penicillins and cephalosporins. The angioedema rarely caused by angiotensin-converting enzyme inhibitors is also like a type I reaction. Therapy includes epinephrine, antihistamines, and supportive care, especially respiratory support if needed.

4.2.2 Type II Hypersensitivity Reactions

Type II reactions are cytolytic reactions involving *IgG or IgM complement-mediated* lysis. Examples of drug-related type II reactions are clozapine agranulocytosis and Coombs positive hemolytic anemia induced by α-methyldopa. In the case of clozapine, prescriptions of clozapine are routinely "bundled" with regular monitoring of complete blood count (CBC) to monitor for agranulocytosis. Prescriptions are filled only with documentation of CBC monitoring.

4.2.3 Type III Hypersensitivity Reactions

Type III reactions are antibody complex reactions that involve *complement-fixing IgG or IgM* antibodies. Antibody complex can deposit in tissues with a variety of consequences. A classic type III reaction is serum sickness from penicillin or sulfonamides. Serum sickness presents with urticarial skin eruptions, arthralgia/arthritis, lymphadenopathy, and fever. Other examples of type III reactions include drug-induced lupus (hydralazine, isoniazid, procainamide), vasculitis (phenytoin, penicillins), Stevens-Johnson syndrome, and toxic epidermal necrolysis.



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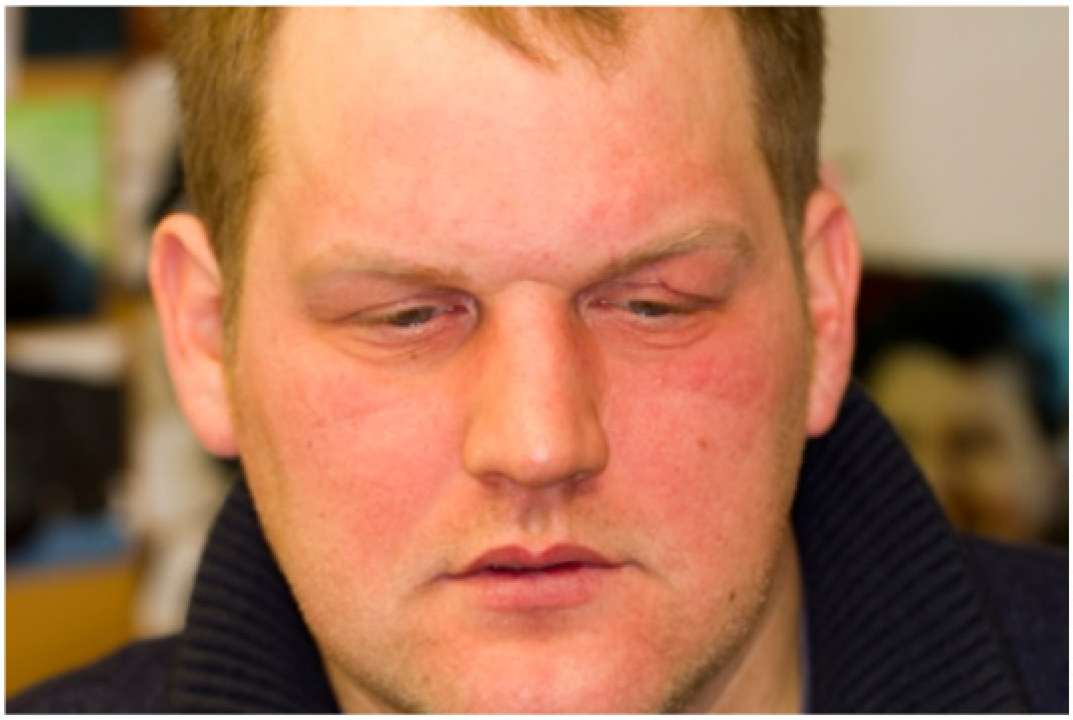
Alexander Heinrichy/doc-stock/Visuals Unlimited, Inc.

▲**Figure 12-4.2A** Type I Reactions: Penicillin-Induced Cutaneous Eruptions



Dr. Hercules Robinson / Phototake, Inc.

▲**Figure 12-4.2B** Type III Reaction: Phenytoin-Induced Vasculitis

4.2.4 Type IV Hypersensitivity Reactions

Type IV reactions are T-cell-mediated skin reactions that are often referred to as "delayed hypersensitivity." The most common triggers of type IV are poison ivy and latex. Rarely, topical medications such as neomycin induce delayed hypersensitivity reactions.

5 Toxicity of Drugs in Pregnancy and Breast-Feeding

Many agents are toxic to the developing fetus and infants. When taken by mothers these agents can bridge the placental barrier to reach developing fetus or enter the breast milk of nursing mothers.

5.1 Risks Associated With Drugs in Pregnancy

The use of medications and other drugs during pregnancy carries the risk of adverse effects to the developing fetus. The benefits of medication therapy during pregnancy then need to be weighed against these potential risks.

5.1.1 Types of Fetal Toxicity

Drugs taken by the pregnant mother can potentially harm the developing fetus, increasing the risk of congenital anomalies ("teratogenicity"), damaging fetal organs (such as radioactive iodine and the fetal thyroid gland), or causing physiologic effects.

▼**Table 12-5.1** Fetal Toxicities

Drug	Trimester	Effect
ACE inhibitors	All, especially second and third	Renal damage
Aminopterin	First	Multiple gross anomalies
Amphetamines	All	Suspected abnormal developmental patterns, decreased school performances
Androgens	Second, third	Masculinization of female fetus
Antidepressants, tricyclic	Third	Neonatal withdrawal symptoms have been reported in a few cases with clomipramine, desipramine, and imipramine
Barbiturates	All	Chronic use can lead to neonatal dependence
Busulfan	All	Various congenital malformations; low birth weight
Carbamazepine	First	Neural tube defects
Chlorpropamide	All	Prolonged symptomatic neonatal hypoglycemia
Clomipramine	Third	Neonatal lethargy, hypotonia, cyanosis, hypothermia
Cocaine	All	Increased risk of spontaneous abortion, abruptio placentae, and premature labor; neonatal cerebral infarction, abnormal development, and decreased school performance
Cyclophosphamide	First	Various congenital malformations
Cytarabine	First, second	Various congenital malformations
Diazepam	All	Chronic use may lead to neonatal dependence
Diethylstilbestrol	All	Vaginal adenosis, clear cell vaginal adenocarcinoma
Ethanol	All	Risk of fetal alcohol syndrome and alcohol-related neurodevelopmental defects

(continued on next page)

▼Table 12-5.1 Fetal Toxicities *(continued)*

Drug	Trimester	Effect
Etetinate	All	High risk of multiple congenital malformations
Heroin	All	Chronic use leads to neonatal dependence
Iodide	All	Congenital goiter, hypothyroidism
Isotretinoin	All	Extremely high risk of CNS, face, ear, and other malformations
Lithium	First, third	Ebstein's anomoly, neonatal toxicity after third trimester
Methadone	All	Chronic use may lead to neonatal abstinence
Methotrexate	First	Multiple congenital malformations
Methylthiouracil	All	Hypothyroidism
Metronidazole	First	May be mutagenic (from animal studies; there is no evidence for mutagenic or testagenic effects in humans)
Misoprostol	First	Mobius sequence
Mycophenolate mofetil	First	Major malformations of the face, limbs, and other organs
Organic solvents	First	Multiple malformations
Penicillamine	First	Cutis laxo, other congenital malformations
Phencyclidine	All	Abnormal neurologic examination, poor suck reflex and feeding
Phenytoin	All	Fetal hydratoin syndrome
Propylthiouracil	All	Congenital goiter
Smoking (constituents of tobacco smoke)	All	Intrauterine growth retardation; prematurity; sudden infant death syndrome; prenatal complications
Selective serotonin reuptake inhibitors (SSRs)	Third	Neonatal abstinence syndrome, persistent pulmonary hypertension of the newborn
Tamoxifen	All	Increased risk of spontaneous abortion or fetal damage
Tetracycline	All	Discoloration and defects of teeth and altered bone growth
Thalidomide	First	Phocomelia (shortened or absent long bones of the limbs) and many internal malformations
Trimethadione	All	Multiple congenital anomolies
Valproic acid	All	Neural tube defects, cardiac and limb malformations
Wafarin	First	Hypoplastic nasal bridge, chondrodysplasia
	Second	CNS malformations
	Third	Risk of bleeding

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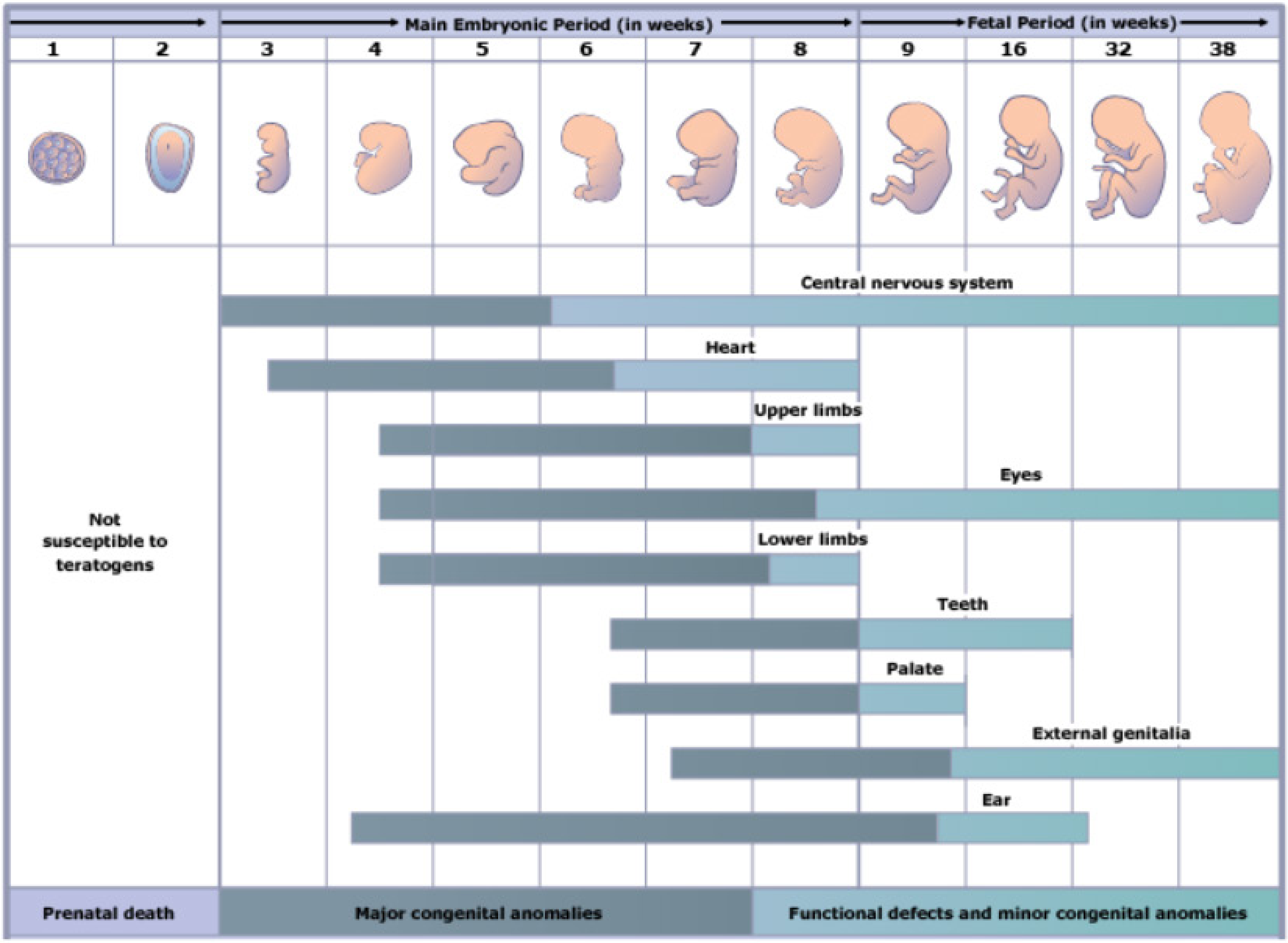
5.1.2 Key Periods of Fetal Organ Development

The critical period of development for most organs is in the first trimester. Thus, the highest risk to the fetus for adverse effects due to teratogens such as thalidomide and lithium occurs during the first trimester. However, the eyes, ears, external genitalia, and brain have longer critical periods of development (with brain and eyes developing throughout pregnancy and after birth). Consequently, teratogens like ethanol that affect these organs can cause birth defects even with second and third trimester exposure.



▲**Figure 12-5.1** Development of Fetal Organs

5.1.3 Thalidomide

Thalidomide is a classic example of a teratogen, causing severe limb anomalies (*"phocomelia,"* literally "seal-like" arms and legs). Decades ago, thalidomide was used in pregnancy to treat nausea and vomiting associated with morning sickness which is most common in the first trimester. Thalidomide was removed from market but has recently reappeared as an *immunomodulatory therapy* for multiple myeloma and leprosy. Thalidomide prescriptions are restricted in women in child-bearing age to those who have demonstrated birth control measures.

5.1.4 Retinoids

Retinoids are vitamin A derivatives used for treatment of acne or autoimmune disorders such as psoriasis. Examples include isotretinoin and etretinate. Retinoids are contraindicated throughout pregnancy due to the risk of birth defects involving limbs, ears, face, and the brain. Pregnant women are advised to use topical benzoyl peroxide or erythromycin instead of retinoids for acne control.

5.1.5 Endocrine Drugs

Danazol is an androgenic drug used to treat endometriosis. Exposure of female fetuses to danazol or related androgenic drugs can cause masculinization of external genitalia. Diethylstilbestrol is a drug discontinued decades ago that caused genitourinary abnormalities following fetal exposure. Some women who were exposed to diethylstilbestrol as fetuses developed unusual cancers as teens and young adults, especially clear-cell adenocarcinoma of the vagina, an otherwise extremely rare tumor.

5.1.6 Thyroid Medications

Treatment of hypothyroidism in pregnancy with thyroid hormone is generally straightforward. *Treatment of hyperthyroidism is much more difficult* because the common therapies all carry risk to the fetus. Thyroid surgery carries obvious risks and is generally attempted only if needed for severe hyperthyroidism during the second trimester. Radioactive iodine destroys the developing thyroid gland and is contraindicated in pregnancy. Iodide (non-radioactive) can lead to neonatal goiter that can impinge on the airway. The safest treatments are propylthiouracil and methimazole. *Propylthiouracil* is preferred because it crosses the placental barrier to a lesser extent than methimazole.

5.1.7 Anticonvulsants

Treatment of epilepsy in pregnancy is quite challenging because a number of *commonly used anticonvulsants are known teratogens*. The risk to the fetus is greatest when these are given during the first trimester. However, seizures in pregnancy are also quite dangerous to the fetus so there is a delicate risk-benefit assessment that physicians must evaluate. Given that a number of the anticonvulsant medications increase liver metabolism and may impact folic acid metabolism, it is especially important that pregnant women taking anticonvulsants take supplements of *folic acid* to lower the risk of neural tube defects such as spina bifida associated with low folic acid. It is also worth keeping in mind that anticonvulsants may be prescribed for other purposes (e.g., bipolar disorder and trigeminal neuralgia) that may be treated in pregnancy.

Phenytoin Use in pregnancy, especially first trimester, is associated with the *fetal hydantoin syndrome* which can present with a wide range of anomalies, including intrauterine growth retardation, microcephaly, craniofacial abnormalities, hypoplastic fingernails or toes, developmental delay, and mental retardation.

Carbamazepine Use during the first trimester of pregnancy is associated with head and facial deformities and an increased risk of *neural tube defects*.

Phenobarbital Use during pregnancy is associated with a relatively small but significant increased risk of birth defects, including neural tube defects. The risks of defects are lower than those of *phenytoin* and *carbamazepine*.

Valproic Acid (Valproate) Use in pregnancy carries significant risk of birth defects, including spina bifida, cleft palate, atrial septal defect, hypospadias (abnormal urethral opening in boys), and polydactyly (extra toes or fingers).

Lamotrigine Has the best safety record in pregnancy of all anticonvulsants on the market. This drug has become the treatment of choice for epilepsy during pregnancy, provided it can control maternal seizures.

5.1.8 Lithium

Lithium is a treatment for bipolar disorder. Use of lithium during the first trimester is associated with the Ebstein anomaly of the tricuspid valve. For treatment of bipolar disorder during pregnancy, *lamotrigine* is a safer choice. Fetal echocardiography may be performed if lithium use does occur during pregnancy.

5.1.9 Chemotherapy

Cancer chemotherapy is generally avoided in pregnancy due to the potential for *teratogenicity*, increased risk of cancers later in life for the exposed fetus, and direct organ toxicity. Chemotherapeutic agents are also used for indications other than cancer treatment (as in severe Crohn disease, rheumatoid arthritis, or psoriasis).

Cyclophosphamide Used both for cancer chemotherapy and treatment of autoimmune disorders. Cyclophosphamide use in pregnancy has been associated with a wide range of birth defects including finger/toe anomalies, gastrointestinal defects, coronary vessel abnormalities, eye defects, and microcephaly.

Methotrexate Used both for cancer chemotherapy and treatment of autoimmune disorders. Methotrexate is contraindicated in pregnancy due to very *high risk for pregnancy termination* or birth defects, such as limb anomalies. The embryotoxic effects of methotrexate are used therapeutically to manage ectopic pregnancy without surgical intervention.

5.1.10 Ethanol

Heavy consumption of ethanol during pregnancy is associated with *fetal alcohol syndrome*, which may present as intrauterine growth retardation, microcephaly, and craniofacial abnormalities such as a thin upper lip and smooth *philtrum*.

5.1.11 Cocaine

Cocaine use in pregnancy can cause a number of problems. The *vasoconstrictive effects* of cocaine impact blood flow to the placenta and fetus, increasing the chances of fetal growth retardation and placental abruption (detachment of placenta from the uterine wall). Cocaine use in pregnancy increases risks of miscarriage, prematurity, respiratory distress syndrome, and fetal bowel infarction.

5.1.12 Opioids

Opioids include a range of prescription and illegal drugs. Abuse of prescription opioids is an increasing problem especially with the large number of prescriptions in the United States for *hydrocodone* and *oxycodone*. The major impact of opioids on the fetus is physiologic (respiratory depression and dependence), and the use of these drugs at any point in pregnancy should be limited if possible. Infants born to mothers with heavy opioid use may present with a neonatal withdrawal (abstinence) syndrome of irritability, high-pitched cry, seizures, fever, diarrhea, and vomiting. Management may require treatment with a long-acting opioid such as *methadone* to lessen withdrawal symptoms.

5.1.13 Antihypertensives

Treatment of hypertension in pregnancy can be challenging. Some of the most common antihypertensive agents have potential problems in pregnancy.

Angiotension Converting Enzyme (ACE) Inhibitors and Angiotensin II Receptor Blockers These antihypertensives are very commonly used antihypertensives. However, use of both classes of drugs in the first trimester has been associated with major congenital malformations and fetal demise. In the second and third trimesters, these drugs interfere with amniotic fluid formation and can lead to *oligohydramnios* (deficiency of amniotic fluid) and *Potter syndrome* (morphologic birth defects).

α-Methyldopa Is seldom used outside pregnancy, but for decades has been a safe choice for management of mild to moderate hypertension in pregnancy.

Hydralazine Is a vasodilator that acts primarily on arteries and arterioles. Hydralazine is used for the management of moderate to severe hypertension in pregnancy, including the hypertension associated with pre-eclampsia or eclampsia. Side effects of hydralazine include *lupus-like syndrome*.

Labetalol Is a combined α/β-adrenergic antagonist. Like hydralazine, labetalol is used for management of moderate to severe hypertension in pregnancy.

5.1.14 Anticoagulant and Antiinflammatory Agents

Aspirin and Nonsteroidal Antiinflammatory Drugs (NSAIDs) These agents block the formation of prostaglandins. This can cause problems by interfering with prostaglandin E_1 (PGE_1), leading to constriction of the fetal ductus arteriosis and potentially serious complications. However, the NSAID *indomethacin* is sometimes used cautiously to slow pre-term labor. Indomethacin is also used to close off ductus arteriosis in premature infants. In general, acetaminophen is a safer choice than NSAIDs for treatment of inflammation and pain in pregnancy.

Warfarin Crosses the placenta and is contraindicated in pregnancy. When used in the first trimester, warfarin can cause birth defects including nasal hypoplasia, spine abnormalities, and brachydactyly (short fingers and toes). Warfarin used throughout pregnancy carries the risk of fetal bleeding.

Heparin Is made up of large, charged molecules and does not cross the placenta. In general, heparin is the *preferred anticoagulant for treatment of blood clotting disorders in pregnancy*, as are seen in recurrent miscarriages and Factor V Leiden. Low-molecular heparins such as enoxaparin are often used, although unfractionated heparin is also a possible choice.

5.1.15 Antibiotics

Many of the common antibiotics (penicillins, clindamycin, erythromycin) are safe during pregnancy. However, several classes are problematic.

Tetracyclines Include tetracycline, doxycycline, and minocyline. Tetracyline is known to cause yellow discoloration of teeth when used in childhood. Fetal exposure can lead to *teeth and skeletal malformations*.

Fluoroquinolones There are safety concerns with using fluoroquinolones during pregnancy, especially due to the known risk of *cartilage damage* associated with use in childhood. However, the risk of teratogenicity appears to be low.

5.2 FDA Drug Pregnancy Categories

The FDA developed a classification system for drug risk during pregnancy. These categories explain possible risks and their frequency of occurrence.

5.2.1 Category A

Category A is for drugs for which adequate and well-controlled human studies show no risk to fetuses. Very few drugs fit in this category. An example is prenatal vitamins.

5.2.2 Category B

Category B is for drugs that are probably safe, based on animal studies, limited controlled studies in pregnant women, or long-term observation. Examples include erythromycin, penicillin, and α-methyldopa.

5.2.3 Category C

Category C includes many medications on the market. There are potential health risks in humans based on animal studies but there are no adequate human studies. These drugs should be used with caution, but benefits may outweigh risks. Examples include bupropion, fluoxetine, and heparin.

5.2.4 Category D

Category D drugs have been demonstrated to cause fetal abnormalities or other fetal risk. However, in some cases, potential benefits may warrant their use in pregnancy. Examples include amiodarone, lithium, phenobarbital, and phenytoin—drugs that all have a narrow therapeutic window.

5.2.5 Category X

Category X drugs are *contraindicated in pregnancy* due to their high risk of teratogenicity or other fetal harm. Examples include etretinate (retinoic acid derivative), methotrexate, radioactive iodine, thalidomide, and warfarin.

▼Table 12-5.2 FDA Teratogenic Risk Categories

Category	Descriptions
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in late trimesters), and the possibility of fetal harm appears remote.
B	Either animal-reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies a potential risk to the fetus.
D	There is positive evidence of human fetus risk, but the benefits from use in pregnant women may be acceptable despite the risk (the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly overweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

5.3 Drugs and Breast-Feeding

Some drugs are capable of crossing into breast milk and potentially affecting the breast-feeding infant.

5.3.1 Amiodarone

Amiodarone is an *iodine-containing drug* that may disrupt infant thyroid function, particularly leading to *hypothyroidism*.

5.3.2 Tetracyclines

Tetracycline can lead to *tooth discoloration* in breast-feeding infants.

5.3.3 Radiopharmaceuticals

Breast-feeding is generally to be avoided in mothers administered radiopharmaceuticals, at least until the drug is cleared from the system.

5.3.4 Antineoplastic and Immunosuppressant Agents

Breastfeeding should be avoided in mothers receiving cancer chemotherapy or immunosuppressant therapy such as cyclophosphamide and methotrexate.

5.3.5 Central Nervous System Depressants

CNS depressants should be used with caution during breast-feeding due to risks of infant sedation and respiratory depression. This includes benzodiazepines, opiates, and phenobarbital.

Chapters 11–12 Review Questions

The following vignette applies to questions 1 and 2.

A 33-year-old female with rheumatoid arthritis is initially treated with ibuprofen, but her joint pain and stiffness are worsening. Her physician prescribes another drug to slow the progression of the disease. This drug helps her rheumatoid arthritis symptoms but she unfortunately develops a number of side effects including dizziness, blurred vision, tinnitus, "halos" around bright lights, and pruritus. Ophthalmologic examination reveals corneal deposits and retinal pigmentation.

1. Which drug *most likely* was prescribed to her?

A. Cyclophosphamide
B. Methotrexate
C. Penicillamine
D. Hydroxychloroquine
E. Etodolac

2. If the patient also developed anemia while on this drug, what enzyme deficiency *most likely* would have predisposed to this complication?

A. Glucose-6-phosphate dehydrogenase
B. N-acetyltransferase
C. α1-antitrypsin
D. Dihydrofolate reductase
E. Thymidine synthetase

The following vignette applies to questions 3 and 4.

A 45-year-old male has had several episodes of gout attacks requiring presentation to the emergency department and subsequent inpatient admission. He consistently has had elevated serum uric acid levels.

3. Which of the following therapies would be *most appropriate* for lowering his serum uric levels and thereby reducing the risk of future gout attacks?

A. Colchicine
B. Penicillamine
C. Indomethacin
D. Prednisone
E. Allopurinol

4. What therapy is indicated if the patient's chronic gout proves refractory to diet modification and standard medication therapies?

A. Pegloticase
B. Methotrexate
C. Colchicine
D. Aspirin
E. Hydroxychloroquine

Review Questions Chapters 11–12

The following vignette applies to questions 5 and 6.

A 4-year-old male is brought to a medical clinic because of an episode of sudden vigorous vomiting. His mother also has noticed that the boy has been acting strangely. The child complains that "his tummy hurts." Physical examination shows a pale child with weakness in his hands and feet. Pupillary examination is normal.

5. What is the most likely toxic exposure for this patient?

A. Arsenic
B. Mercury
C. Acetaminophen
D. Organophosphate insecticide
E. Lead

6. What is the best medical therapy for this patient?

A. $CaNa_2$-EDTA
B. Deferoximine
C. *N*-acetylcysteine
D. Atropine
E. Pralidoxime

The following vignette applies to questions 7 and 8.

A 5-year-old female is brought to the emergency room by her parents because she is suffering from severe nausea, hematemesis, and abdominal pain. She had been playing with a bottle of "candy" in her parents' bedroom and an open bottle of medicine was found on the floor. Physical examination shows the child to be lethargic and disoriented, markedly tachypneic, flushed in the face, and feverish.

7. What is the recommended treatment?

A. Sodium bicarbonate infusion
B. *N*-acetylcysteine
C. Intravenous magnesium
D. Naloxone
E. EDTA

8. What do you expect the arterial blood gas results to show?

A. Metabolic alkalosis and respiratory acidosis
B. Metabolic acidosis and respiratory alkalosis
C. Metabolic acidosis and respiratory acidosis
D. Metabolic alkalosis and respiratory alkalosis
E. Metabolic alkalosis only

Chapters 11–12 Review Answers

1. The correct answer is D. *Hydroxychloroquine* (Plaquenil) is a DMARD that has the potential adverse effect of *causing corneal and retinal deposits leading to vision disturbances*. The other drugs listed also can be used in rheumatoid arthritis treatment but are not commonly associated with ophthalmic side effects. *Regular ophthalmologic examinations* are recommended for patients on hydroxychloroquine therapy.

2. The correct answer is A. Glucose-6-phosphate dehydrogenase (G6PD) deficiency. Patients with G6PD deficiency are susceptible to hemolytic anemia when exposed to agents that promote oxidative stress, including chloroquine, hydroxychloroquine, dapsone, mefloquine, and primaquine. The other enzymes listed are not involved with the adverse effects of hydroxychloroquine. Prior to initiating hydroxychloroquine therapy, the physician should question the patient on any prior history that might suggest G6PD deficiency-related hemolytic anemia.

3. The correct answer is E. Allopurinol is used for the management of chronic gout and works by inhibiting xanthine oxidase, an enzyme that converts xantine to uric acid. Colchicine is used in acute gout attacks to reduce inflammation by inhibition of neutrophils. Indomethacin also is used in reducing inflammation in acute gout attacks. Corticosteroids such as prednisone can be used in acute gout attacks, either systemically or by direct injection into the gouty joint. Pencillamine is not used in gout management.

4. The correct answer is A. Pegloticase is a recombinant uricase approved for the management of chronic gout refractory to diet modification and standard medical therapies (e.g., allopurinol). The other agents are either used for acute gout (aspirin and colchicine) or not used for management of gout at all (methotrexate and hydroxychloroquine). The major limitation to pegloticase is its expense (thousands of dollars per round of therapy), which limits use to cases that fail to respond to standard therapy.

5. The correct answer is E. Lead. The clinical presentation on its own could be due to a variety of causes including toxic exposure (lead or organophosphate insecticide), infection, or metabolic disorder. In terms of toxic ingestions, lead is most likely with the normal papillary examination inconsistent with organophosphate poisoning, where pinpoint pupils would be expected. The diagnosis would be made by whole blood lead concentration measurement.

6. The correct answer is A. $CaNa_2$-EDTA. The standard therapy for lead toxicity is chelation therapy with $CaNa_2$-EDTA. The other drugs are antidotes for other poisonings: iron (deferoximine), acetaminophen (*N*-acetylcysteine), and organophosphate (atropine and pralidoxime).

Review Answers Chapters 11–12

7. The correct answer is A. Sodium bicarbonate. This child presents with the following symptoms: nausea, hematemesis, abdominal pain, lethargy, disorientation, tachypnea, facial flushing, and fever. Some of these symptoms are nonspecific (e.g., abdominal pain and disorientation) and could be found in a variety of ingestions. For example, iron poisoning could produce the gastrointestinal symptoms seen in this child, and many drugs that affect the central nervous system can produce altered mental status and disorientation. However, the *marked tachypnea* and *fever* are less common in drug toxicity and are most suggestive of *salicylate toxicity* when combined with the other symptoms in this child. Sodium bicarbonate infusion speeds renal elimination of aspirin. There is no specific antidote to aspirin overdose. Management includes replacement of fluid losses, administration of activated charcoal (most useful if ingestion is within one to two hours of presentation), antacids to minimize gastrointestinal upset, and sodium bicarbonate to enhance renal elimination. Alkalinization of urine increases ionization of aspirin and reduces its reabsorption from the renal tubules back into the systemic circulation. For the other choices, *N*-acetylcysteine is an antidote for acetaminophen overdose, naloxone is an antidote for opiate overdose, and EDTA is used as a heavy metal chelator. Magnesium is used to manage certain cardiac arrhythmias, especially ventricular tachycardia.

8. The correct answer is B. Metabolic acidosis and respiratory alkalosis. Aspirin can produce a complex acid-base disorder. The metabolic acidosis is a result of aspirin being a weak acid. The respiratory alkalosis is from rapid breathing, a result of aspirin having a direct stimulatory effect on the breathing center in the brainstem. The respiratory alkalosis is not simply a response to metabolic acidosis. The combined acid-base disorder can produce a "normal" pH, something that would be expected if the primary disorder is metabolic acidosis while respiratory alkalosis is a response to the acidosis. Patients with aspirin toxicity will often reveal *very low bicarbonate (metabolic acidosis)* and *pCO_2* (respiratory alkalosis).

Clinical Case 1

History

A 30-year-old female presents to her primary care physician with complaints of several months of lethargy and "feeling down." She is diagnosed with major depression and started on a dose of 20 mg fluoxetine (Prozac) per day. However, two weeks later she phones the physician's office stating that she is feeling very jittery and so returns to the clinic.

Physical Findings

Resting pulse of 130 bpm

Laboratory Results

Plasma level of fluoxetine + norfluoxetine (metabolite) returns with elevated reading of 900 ng/mL (reference range 120–300)

Diagnosis: Slow metabolizer of CYP2D6

Discussion

The clinical scenario is strongly suggestive for a problem involving the metabolism of fluoxetine. The patient is started on a modest dose of fluoxetine yet within two weeks has symptoms of fluoxetine excess together with very elevated plasma fluoxetine levels. This could be caused by a genetic defect affecting fluoxetine levels, a drug-drug interaction, or liver failure. In an otherwise healthy 30-year-old, liver failure is not likely. Fluoxetine is predominantly metabolized by CYP2D6, an enzyme which shows genetic variation. CYP2D6 "slow metabolizers" have little or no CYP2D6 activity and can see toxicity with drugs that require CYP2D6 for clearance such as fluoxetine, paroxetine, beta-blockers, and some antipsychotics. Alternatively, the patient could be taking a drug that inhibits CYP2D6 activity. Powerful CYP inhibitors include ketoconazole, cimetidine, and erythromycin. There are also some drugs that depend on CYP2D6 for activation. Codeine is an example, being essentially a prodrug that depends mainly on CYP2D6 for conversion to morphine. Thus, patients with low CYP2D6 activity will have poor therapeutic response to codeine due to lack of conversion to morphine. Another example is tamoxifen, an antiestrogen used for treatment of estrogen receptor-positive breast cancers.

Clinical Case 2

History

A four-year-old boy is brought into the emergency room by his parents after he was found near an open bottle of antifreeze. There was antifreeze on his clothes and it appeared he drank some. Approximately one-fourth of the previously unopened bottle is missing. Upon presentation to the emergency room, the child is alert but answers questions with confused responses.

Physical Findings

Patient is alert but has difficulty following directions. His heart rate is 95 bpm and respiratory rate is 12/min. Blood pressure is 115/75 mmHg.

Laboratory Results

Serum chemistries:

- Sodium 145 mEq/L
- Potassium 3.8 mEq/L
- Chloride 105 mEq/L
- Bicarbonate 7 mEq/L
- BUN 13 mg/dL.

Arterial blood gas:

- pH 7.19
- pCO_2 32 mm Hg
- pO_2 110 mg Hg
- HCO_3^- 13 mEq/L

Diagnosis: Ethylene glycol poisoning

Discussion

Ingestion of antifreeze containing ethylene glycol is a medical emergency requiring urgent therapy. The basic laboratory workup would include serum electrolytes (allowing for calculation of anion gap), arterial blood gas analysis, and serum osmolality. If available, a direct determination of ethylene glycol plasma concentration is ideal but most hospital laboratories do not have this capability. Keep in mind that ethylene glycol will not be detected by serum/plasma ethanol measurement. The classic presentation will be an anion-gap metabolic acidosis with increased serum osmolality (osmolal gap).

The specific organ damage caused by ethylene glycol is to the kidney via accumulation of metabolite oxalic acid, which combines with calcium to crystallize in the renal tubules. Fomepizole is a specific inhibitor of alcohol dehydrogenase that serves as an antidote for ethylene glycol. An alternative antidote is ethanol, which competes with ethylene glycol for alcohol dehydrogenase. Patients that present to clinical attention many hours after ingestion should receive renal dialysis to clear ethylene glycol and its toxic metabolites. The downside to dialysis is that it is an invasive procedure.

Clinical Case 3

History

A 37-year-old male is brought to the emergency room by ambulance after collapsing at work at a metal-plating factory. He reported a headache prior to collapsing.

Physical Findings

Unresponsive to external stimuli, has a bitter almond smell, and is giving agonal respirations (gasping, labored breathing). Heart rate is 165 bpm and blood pressure is 90/50.

Laboratory Results

- Venous blood gas analysis pO_2 = 80 torr
- Arterial blood gas analysis pO_2 = 90 torr

Diagnosis: Cyanide poisoning

Discussion

Cyanide poisoning is a life-threatening condition that requires prompt medical attention. Cyanide is used in photographic, fumigation, and metal-plating industries. Cyanide is a rapid acting poison that binds to cytochrome oxidase and blocks of use of oxygen in cellular respiration. The inability to use oxygen for cellular respiration can lead to an unusual blood gas profile with almost identical venous and arterial pO_2 values.

In addition to supportive therapy (e.g., supplemental oxygen), several antidotes are available. Amyl or sodium nitrite are the traditional antidotes for acute cyanide poisoning. A newer alternative is hydroxycobalamin, a derivative of vitamin B12. Sodium thiosulfate is used to prevent chronic cyanide poisoning, as can occur in sodium nitroprusside therapy. For the patient in the case, rapid supportive care and administration of a nitrite or hydroxycobalamin is warranted.

Clinical Case 4

History

A 16-year-old boy has finished induction chemotherapy for treatment of acute lymphoblasatic leukemia (ALL) and is now being switched to consolidation chemotherapy that includes 6-mercaptopurine. His induction chemotherapy went well and blood cell counts recovered to low normal range. However, four days after starting the consolidation regimen, he begins to feel very ill and notices that his gums are bleeding. His parents take him to the emergency room after measuring his body temperature at 39.6°C.

Physical Findings

Patient is alert and conscious but looks extremely fatigued. He appears to be laboring while breathing. His gums are bleeding in multiple spots and there are numerous petechiae on his trunk and arms. His heart rate in 100 bpm and respiratory rate is 28/min. Blood pressure is 105/60 mm Hg.

Laboratory Results

Serum chemistries:

- Sodium 135 mEq/L (ref. range 135–145)
- Potassium 4.9 mEq/L (3.5–5.0)
- Chloride 102 mEq/L (95–107)
- CO2 27 mEq/L (24–32)
- BUN 30 mg/dL (10–20)
- Creatinine 0.6 mg/dL (0.6–1.2)

Arterial blood gas:

- pH 7.45 (7.32–7.42)
- pCO_2 22 mm Hg (30–40)
- pO_2 100 mg Hg (80–100)
- HCO_3^- 25 mEq/L (22–26)

Complete blood count:

- WBC 0.2 k/mm^3 (3.7–10.5), differential shows normal percentages but absolute neutropenia, lymphopenia, and monocytopenia.
- Hemoglobin 5.1 g/dL (13.2–17.7)
- Hemocrit 16 % (40–55)
- Platelets 8 k/mm^3 (150–400)

Diagnosis: Bone marrow suppression due to adverse reaction to 6-mercaptopurine

Clinical Case 4

(continued)

Discussion

This patient had just completed induction chemotherapy that was potentially toxic to the bone marrow. However, his blood counts had recovered prior to starting consolidation therapy. On presentation to the emergency room, he has history and physical evidence of pancytopenia: bleeding gums and petechiae (low platelets), fatigue, rapid breathing (anemia), and fever/infection (neutropenia).
This is confirmed by his complete blood count. The evidence is suspicious for toxicity of 6-mercaptopurine. Approximately 1 in 300 Caucasians do not metabolize 6-mercaptopurine efficiently due to genetic defect in thiopurine methyltransferase (TPMT). Although genetic or phenotypic testing of TPMT is available, it is not always performed prior to starting 6-mercaptopurine. For this patient, 6-mercaptopurine should be stopped immediately and supportive therapy should be started, including platelet and RBC transfusions, and antibiotic therapy for infection. This patient is at high risk for severe bleeding and infection complications.

Clinical Case 5

History

A 42-year-old female with a history of rheumatoid arthritis for 5 years presents to her primary care physician. She has tried many therapies but has found the best relief with aspirin. However, she is now taking up to four 325 mg tablets of aspirin per day. In the last two weeks, she has felt sharp epigastric pain, particularly around meal times. She also has noticed that her stools have been tar-colored and foul smelling.

Physical Findings

Patient is alert and conscious but looks pale and anxious. Her heart rate is 95 bpm and respiratory rate is 18/min. Blood pressure is 100/60 mm Hg.

Laboratory Results

Serum chemistries:

- Sodium 137 mEq/L (ref. range 135–145)
- Potassium 4.4 mEq/L (3.5–5.0)
- Chloride 101 mEq/L (95–107)
- CO_2 28 mEq/L (24–32)
- BUN 20 mg/dL (10–20)
- Creatinine 0.4 mg/dL (0.6–1.2)

Complete blood count:

- WBC 8.8 k/mm3 (3.7–10.5), differential is normal
- Hemoglobin 11.1 g/dL (13.2–17.7)
- Hemocrit 32.9% (40–55)
- Platelets 355 k/mm3 (150–400)

Imaging

Due to the suspicion of peptic ulcer disease, the patient is referred for esophagogastroduodenoscopy (EGD) which reveals a 2 cm ulcer along the lesser curvature of the stomach. This ulcer shows evidence of recent bleeding.

Diagnosis: Peptic ulcer disease, likely related to aspirin use

Clinical Case 5

(continued)

Discussion

NSAIDs, particularly salicylates, are a common risk factor for development of peptic ulcer disease. This patient is at high risk due to the use of high-dose aspirin for an extended period of time. Even prior to the EGD, there are several signs and symptoms in this patient that strongly suggest peptic ulcer disease including epigastric pain (associated with meals), anemia (possibly underlying her paleness), and melena. The first step is to reduce or eliminate her salicylate use. Referral to rheumatologist could be helpful in seeing whether other therapies can manage her arthritis symptoms. Sucralfate could be prescribed to help her ulcer heal and reduce risk of more serious complications. Misoprostol may help in increasing gastric mucus production and limit damage caused by NSAIDs. If misoprostol is used in this patient, she should first have pregnancy test to make sure she is not pregnant given that misoprostol has effects on the uterus that can lead to abortion.

Clinical Case 6

History

A 59-year-old man is brought to the emergency department by police after he was found unconscious in the street. No other history is known. There is no external evidence of ethanol or drug use.

Physical Findings

Patient is unconscious with a rectal temperature of 40°C (104°F). Pupils are 4 mm and equally reactive to light. The patient's neck is stiff; when the neck is moved, the patient moans with pain.

Laboratory Results

Serum chemistries:

- Sodium 141 mEq/L (ref. range 135–145)
- Potassium 3.9 mEq/L (3.5–5.0)
- Chloride 100 mEq/L (95–107)
- CO_2 26 mEq/L (24–32)
- BUN 25 mg/dL (10–20)
- Creatinine 0.6 mg/dL (0.6–1.2)
- Glucose 105 mg/dL (65–100)
- Anion gap 15 (< 16)

Serum osmolality 295 mOsm/kg (280–300)

Arterial blood gas:

- pH 7.29 (7.32–7.42)
- pCO_2 49 mm Hg (30–40)
- pO_2 81 mg Hg (80–100)
- HCO_3^- 25 mEq/L (22–26)

Ethanol 0 mg/dL

Urine drug of abuse panel: negative for amphetamines, benzodiazepines, cocaine, opiates, and tetrahydrocannabinol.

Cerebrospinal fluid analyses:

- Appearance: Turbid
- WBC 950/µL (0-5), 95% neutrophils, 5% mononuclear cells
- Glucose 20 mg/dL (40–75)
- Protein 200 mg/dL (15–25)
- Gram-positive diplococcic seen on Gram stain of CSF

Diagnosis: Bacterial meningitis due to *Streptococcus pneumoniae*

Discussion

The differential diagnosis for an adult patient presenting unconscious with no history is broad and includes ethanol/drug intoxication, hypoglycemia, and meningitis. Often such patients will empirically be given naloxone, thiamine, and dextrose in the emergency setting. These therapies are unlikely to cause harm but can rapidly reverse opiate overdose, Wernicke encephalopathy, and hypoglycemia, respectively. For the patient in the case, the neck stiffness is suspicious for meningitis. The cerebrospinal fluid studies are consistent with bacterial meningitis (turbid, low glucose, high protein, high white blood count with neutrophils), further supported by identification of gram-positive diplococci. *Streptococcus pneumoniae* is the most common cause of bacterial meningitis for this age of patient. Other possibilities for bacterial meningitis in the adult population include *Neisseria meningitidis* (more typical in younger adults), *Haemophilis influenzae*, and *Listeria monocytogenes*. Fungal meningitis is a possibility but much less common than bacterial meningitis.

The typical empiric antimicrobial therapy for presumptive bacterial meningitis in an adult would be a third-generation cephalosporine that can penetrate the blood-brain barrier. The most common example would be ceftriaxone. Ceftriaxone would cover *N. meningitidis* and *H. influenzae* in addition to *S. pneumoniae*.

Clinical Case 7

History

A 35-year-old male is evaluated in the emergency department for recent episode of hemoptysis and shortness of breath. He was diagnosed with Hodgkin lymphoma 8 months ago and completed a full course of chemotherapy followed by radiation therapy to the chest.

Physical Findings

Patient is alert but looks ill.

- Temperature: 38.2°C
- Heart rate: 95 bpm
- Blood pressure; 125/75 mm Hg
- Respiration rate: 23/min

Laboratory Results

Serum chemistries:

- Sodium 136 mEq/L (ref. range 135–145)
- Potassium 4.5 mEq/L (3.5–5.0)
- Chloride 98 mEq/L (95–107)
- CO_2 26 mEq/L (24–32)
- BUN 15 mg/dL (10–20)
- Creatinine 0.8 mg/dL (0.6–1.2)
- Glucose 70 mg/dL (65–100)
- Anion gap 12 (< 16)

Complete blood count:

- WBC 13.5 k/mm^3 (3.7–10.5), 65% lymphocytes
- Hemoglobin 11.8 g/dL (13.2–17.7)
- Hemocrit 35.7% (40–55)
- Platelets 120 k/mm^3 (150–400)

Sputum sample demonstrates acid-fast bacteria. Sputum also sent for culture, eventually grew out *Mycobacterium tuberculosis.*

Chest X-ray: Cavitary lesion in right upper lobe

Diagnosis: Tuberculosis

Clinical Case 7

(continued)

Discussion

This patient is likely immunocompromised from his Hodgkin disease and the subsequent chemotherapy and radiation treatment. This puts him at higher risk for a variety of infections, including bacterial, mycobacterial, and fungal. The laboratory studies show that he is also anemic and mildly thrombocytopenic. The key finding is the cavitary lesion in his lung which is strongly suggestive of tuberculosis, although fungal infection could produce a similar picture. The ability to identify acid-fast bacteria in the sputum sample is very helpful in this case, as that guides the decision to start anti-mycobacterial therapy. The recommended initial course of therapy would be a four drug regimen (e.g., isoniazid, rifampin, pyrazinamide, and ethambutol) until the drug sensitivity for the patient's tuberculosis strain can be determined. Once antibiotic susceptibilities are known, the patient should be treated with at least two drugs to which the tuberculosis strain is sensitive to in vitro. An example regimen would be isoniazid and rifampin for 9 months.

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